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PHARMACOLOGIC AND THERAPEUTIC PROPERTIES OF CRYSTALLINE VITAMIN C (CEVITAMIC ACID)

WITH ESPECIAL REFERENCE TO ITS EFFECTS ON THE CAPILLARY FRAGILITY

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The isolation of hexuronic acid from cabbages, orange juice and adrenal cortex by Szent-Györgyi [1] in 1928 opened a new field for investigation, which culminated in 1932 with its identification as crystalline vitamin C, now termed cevitamic acid.[2]

This substance is an odorless, white or yellowish-white crystalline powder, with a melting point of from 189 to 192 C. An outline of its properties follows:

Formula: The acid titration corresponds with the formula $C_6H_8O_6$.[3]

Solubility: It is freely soluble in water and also soluble in acetone, acetic ether and propyl alcohol, and insoluble in ethyl ether and purified petroleum benzine.[4]

Stability: It oxidizes on exposure to air and light. In an inert atmosphere it is quite stable to moderate heat, even in alkaline solution.[5] It is decomposed when heated above 185 C.[3a]

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1. Szent-Györgyi, A.: Biochem. J. **22**:1387, 1928; Nature, London **129**:576, 1932.

2. (*a*) Tillmans, J.; Hirsch, P., and Hirsch, W.: Ztschr. f. Untersuch. d. Lebensmitt. **63**:1, 1932. (*b*) Svirbly, J. L., and Szent-Györgyi, A.: Biol. J. **26**:865, 1932. (*c*) Szent-Györgi, A.: Deutsche med. Wchnschr. **22**:852, 1932. (*d*) Zilva, S. S.: Nature, London **129**:3269, 1932. (*e*) Waugh, W. A., and King, C. G.: J. Biol. Chem. **97**:325, 1932.

3. (*a*) Waugh, W. A.: J. Chem. Educ. **11**:69 (Feb.) 1934. (*b*) Birch, T. W., and Harris, L. J.: Biochem. J. **27**:595, 1933.

4. Sipple, H. L.; Grettie, D. P.; Svirbly, J. L., and King, C. G.: J. Biol. Chem. **94**:483, 1931-1932. Matsuoka, Tomiji: J. Agric. Chem. Soc. Japan **9**:1130, 1933.

5. Herbert, R. W., and others: J. Chem. Soc., Sept. 1933, p. 1270.

Reducing power: It has a high reducing power. This reducing power is the more remarkable since the oxidation of the acid is reversible. It is by this reversible oxidizability that the substance probably exerts its biologic activity. It is oxidized and reduced alternately, giving off and taking up two atoms of hydrogen, thus acting as a hydrogen carrier between different parts of its oxidation system.[6]

Salts formed: Precipitation as lead salt from an alcohol or water solution is consistent with regard to activity and properties.[3a]

Diffusion: The active factor of vitamin C diffuses rapidly through a collodion membrane.[7]

Effect of light: The vitamin C (reducing substance) in milk is apparently sensitive to visible light.[8]

Color reaction: A slightly alkaline solution acquires, on standing with ferrous sulfate, a dark violet color.[9]

Absorption spectrum: In methyl alcohol and in aqueous solution (20 mg. per liter) an intense band is found at from 260 to 265 microns. In ethyl alcohol and also in acidified aqueous solutions the band occurs at 245 microns.

Optical rotation (with a 10 per cent solution)[10]:

$[\alpha]\ 20/D = 24$ to 25
$[\alpha]\ 22/D = 23$
$[\alpha]\ 24/D = 21.01$

Pigmentation: Cevitamic acid prevents the formation of pigment in the tissue sections.[9a]

Potentiometric studies: In cevitamic acid the —CHOH— group between the two CO groups rapidly gives up 2H at a potential level corresponding approximately to the value $rH_2 17$.[11]

Chemical determination: The method described by Harris and Ray is based on modifications in the use of Tillman's indicator, sodium 2,6-di-chlorophenol indophenol. The essential features are a preliminary extraction process with tri-chloracetic acid, followed by titration in acid solution. These conditions are necessary in order to rule out interference by other reducing substances present in many animal tissues, notably glutathione, which would otherwise render the test of little significance.[12]

Since the original work, this substance has been obtained also from adrenal medulla, corpus luteum, lemon juice, paprika, green pepper,

6. Szent-Györgyi, A.: Nature, London **131**:225 (Feb. 18) 1933. Haworth, W. N.: Chem. & Industry **52**:482 (June 9) 1933.

7. McKinnis, R. B., and King, C. G.: J. Biol. Chem. **87**:615, 1930.

8. Kon, S. K.: Nature, London **132**:64 (July 8) 1933. Mattick, A. T. R., and Kon, S. K.: ibid., p. 446.

9. Schroeder, H.: (*a*) Klin. Wchnschr. **13**:553, 1934; (*b*) Bull. Soc. chim. biol. **4**:83, 1922. Bessonov, N., and Delire, A.: Compt. rend. Acad. d. sc. **196**: 2036 (June 26) 1933.

10. Lowry, T. M., and Pearman, S. A.: J. Chem. Soc., Nov. 1933, p. 1444. Waugh and King.[2e] Waugh.[3a]

11. Wurmser, Rene, and de Loureiro, J. A.: Compt. rend. Soc. de biol. **113**: 543, 1933. Georgescu, I.: J. de chim. phys. **29**:217, 1932. Green, David E.: Biochem. J. **27**:1044, 1933. Waugh (footnotes 2e and 3a).

12. Harris, L. J., and Ray, S. N.: Biochem. J. **27**:303, 1933.

gladiolus, iris, skunk cabbage (Symplocarpus foetidus), parsley, water cress and other sources.

The formula ($C_6H_8O_6$) was accepted, and it was found that less than 1 mg. of this substance a day was enough to keep a guinea-pig free from scurvy. The structural formula, however, has been a matter of considerable study and discussion, principally by Cox and Hirst,[13] Karrer [14] and Micheel.[15] It has since been synthesized.[16]

One of the first questions to arise was whether the antiscorbutic effects produced by the use of cevitamic acid were due to the inherent properties of a pure substance or whether they came from an attached impurity. The point was made that vitamin C could perhaps be present only as an impurity of cevitamic acid, since the protective dose is so many times greater than that of vitamin A (Ratte), B (Taube) and D (Ratte). Since it may be pointed out that vitamin C is much more abundant in nature, providing in the natural diet a supply which is easily adequate, such a conclusion appears unwarranted.

Rygh,[17] at the beginning of 1932, expressed the belief that he had isolated vitamin C from orange juice, and he identified it as methylnornarcotine, which he claimed was an antiscorbutic agent for guinea-pigs. Dalmer and Moll,[18] Bruggeman [19] and Grant, Smith and Zilva [20] were unable to confirm this work. Rygh published further experiments [21] in which he claimed to have demonstrated that while methylnornarcotine prevented scurvy in guinea-pigs it did not enable the animals to live. The simultaneous administration of glycuronic acid, however, in daily doses of 0.5 mg. maintained life. He assumed, on the basis of this experiment on animals, that the guinea-pig fed a diet free from vitamin C is not able to form the glycuronic acid necessary for the maintenance of life and believed that he could draw the further conclusion from his work that hexuronic acid, found by Szent-Györgyi, was antiscorbutic only by virtue of traces of methylnornarcotine which it contained. In the light of much recent work, this does not appear to be correct. The antiscorbutic effect is produced even in the most carefully purified preparations of cevitamic acid. Carefully fractioned crystalli-

13. Cox, E. G.; Hirst, E. L., and Reynolds, R. J. W.: Nature, London **130**: 888, 1932; Chem. & Industry **52**:221, 1933.

14. Karrer, P.: Biochem. Ztschr. **4**:258, 1933; Helvet. chim. acta. **16**:302, 1933.

15. Micheel, F., and Kraft, K.: Nature, London **131**:274, 1933; Ztschr. f. physiol. Chem. **216**:233, 1933.

16. Reichstein, T.: Grussner, A., and Oppenauer, R.: Helvet. chim. acta **16**: 561, 1933.

17. Rygh, O.: Ztschr. f. physiol. Chem. **204**:105, 1932.

18. Dalmer, O., and Moll, T.: Ztschr. f. physiol. Chem. **209**:4 and 211, 1932.

19. Bruggeman, J.: Ztschr. f. physiol. Chem. **211**:3 and 231, 1932.

20. Grant, R. I.; Smith, S., and Zilva, S. S.: Biochem. J. **26**:1628, 1932.

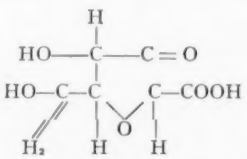
21. Rygh, O., and Rygh, A.: Ztschr. f. physiol. Chem. **211**:275, 1932.

zation of cevitamic acid (Karrer [14]) has shown that it is not possible to get crystals of varying potency. Szent-Györgyi further has obtained, by purification through crystallization, mono-acetone cevitamic acid, which has been found by some workers to have only slightly antiscorbutic potency. After splitting off the acetone fraction the cevitamic acid exhibited its unaltered potency.

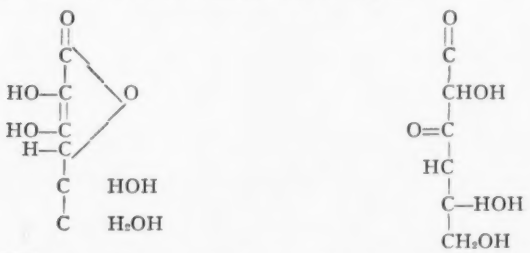
Many investigators [22] have agreed that hexuronic acid has been found completely free from nitrogen. Various other authors [23] have reported that methylnornarcotine together with glycuronic acid is ineffective as an antiscorbutic agent in guinea-pigs. Westin,[24] who examined histologically the animals of Rygh, could discover, according to the tooth method, no evidence of an effect of this combination on the scorbutic appearance of the tooth. Dalmer and Moll [22b] reported that guinea-pigs treated by this method died at the same time as untreated controls and with equally severe scorbutic manifestations.

It would, therefore, appear that at present the weight of evidence is decidedly against the contentions of Rygh in this regard.

Several structural formulas, including the following one suggested by F. Micheel,[25] with what seems to be good substantiation, have been presented.



The formula on the left is believed by Major [26] to be the correct one. An isomer of this is shown on the right.



22. (*a*) Tillmans, J., and Hirsch, P.: Biochem. Ztschr. **250**:312, 1932. (*b*) Dalmer, O., and Moll, T.: E. Merck's Jahresb., 1932, p. 19. Szent-Györgi.[1] Waugh.[2e]

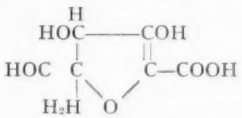
23. Widmark, E. M., and Glimstedt, G.: Ztschr. f. physiol. Chem. **215**:147, 1933. Reschke, J.: ibid., p. 164. Dann, W. J.: Nature, London **131**:24, 1933.

24. Westin, G.: Ztschr. f. Vitaminforsch. **2**:1, 1933.

25. Micheel, F.: E. Merck's Jahresb., 1932, p. 4. Micheel and Kraft.[15]

26. Major, R.: Personal communication to the authors.

The following isomer has also been suggested, but we do not believe that the corresponding chemical has actually been made.[25]



Biologic tests of the antiscorbutic effect of cevitamic acid have led to different conclusions, depending on the several methods used, the difference in the use of the same method, the difference in laboratory conditions, the difference in the potency of citrus fruit juice used, variations in animals used and other factors. Svirbly and Szent-Györgyi [26] found that 0.5 mg. of cevitamic acid corresponded to 1.5 cc. of lemon juice. Birch and his co-workers,[27] using the tooth method, determined that 0.6 mg. of cevitamic acid has the effectiveness of 1 cc. of orange juice. On the other hand, Key and Elphick [28] found that orange juice and lemon juice were equally effective, according to the tooth method. In consideration of the purity of crystalline vitamin C, this seeming paradox must rest with the differences in method, as mentioned previously.

Reports of clinical experience with the use of cevitamic acid have thus far been limited to isolated studies. As is usually the case with a new form of treatment, it has been used in a great variety of conditions. Some of this work has been poorly controlled, and conclusions have been drawn from insufficient evidence, for example, the cessation of bleeding occurring in a single instance in any of the hemorrhagic diseases. This is recognized to be often irregular and capricious. Conclusions founded on such phenomena appear unwarranted. When, however, the results of study of individual cases or of small groups are coordinated and reviewed, such investigations may be of great value.

At a conference on vitamin C held at Darmstadt on April 14, 1934,[29] Professor Stepp of Breslau reported certain effects of vitamin C on various metabolic processes. Following intravenous injections of large amounts of the vitamin, no change was found in the sugar, cholesterol, calcium or phosphorus content of the blood. After several days' administration, a slight increase in the carbon-nitrogen quotient in the urine was found. He reported that injections of 100 mg. of cevitamic acid each day for several days resulted in a definite increase in the amount

27. Birch, T. W.; Harris, L. S., and Ray, S. N.: Nature, London **131**:273, 1933.

28. Key, K. M., and Elphick, G. K.: Biochem. J. **25**:888, 1931.

29. Unpublished minutes of Conference on Vitamin C, Darmstadt, April 14, 1934.

of albumin, which resulted in alteration of the rate of sedimentation of the blood corpuscles. He reported the case of a patient with purpura rheumatica who showed no improvement under any other form of treatment and in whom he was able to bring about a striking disappearance of the tendency to hemorrhage by the intravenous administration of large doses of cevitamic acid. It was reported, also, that Dr. Stalte of the children's clinic in Breslau confirmed these findings in children with Schönlein-Henoch's disease and also in cases of true "morbus maculosis of Werlhof," which was "markedly influenced" by vitamin C, although he did not define what he meant by that.

A variety of additional conditions was reported at this conference as having been influenced favorably by the use of cevitamic acid, e. g., scurvy in childhood, dysentery, leukemia, peritonitis, diphtheria, "hemorrhagic nephritis," acute infections of the respiratory tract, pyuria in childhood (ten cases with nine cures), ununited fractures and certain forms of pigmentation of the skin.[30] It should be stated, however, that these reports were not completed studies but rather informal preliminary observations on the part of a group of workers from throughout Germany. It was fully realized that many of these observations might not be substantiated by further experience.

Professor Gabbe, of Bremen, reported at the same conference a method which permits the determination of the presence of vitamin C in the blood. With this method, he found the normal vitamin C content to be between 0.7 and 1.2 mg. per hundred cubic centimeters of blood. These values rise or fall from 30 to 50 per cent with a higher or lower content of vitamin C in the food. Abnormally low findings were found not only in persons maintained on a diet poor in vitamin C but, in spite of plentiful addition of vitamin C, in persons suffering from severe infections which had lasted for several weeks, e. g., from 0.15 to 0.25 mg. per hundred cubic centimeters in cases of sepsis and typhoid. He felt that these findings indicated a greater metabolic use of vitamins in patients suffering from infection. In patients with carcinoma, values corresponding to the state of nutrition were found in the blood.

Numerous cures of infantile scurvy by the use of cevitamic acid were reported during 1934. Wentzler[31] reported a case in a 6 month old boy in whom signs and symptoms showed a favorable change in six days and who was entirely restored to normal in twenty-one days. The daily dose used was 50 mg. dissolved in the food and taken by mouth. Neumann[32] reported its use in the treatment of a 10 month old child with frank scurvy (Moeller-Barlow's disease). Although there

30. Morawitz, P.: Klin. Wchnschr. **13**:324, 1934. Schroeder, H.: Ann. de E. Merck, 1934, pt. 2, p. 118.

31. Wentzler, E.: Monatschr. f. Kinderh. **59**:451, 1934.

32. Neumann, U.: Deutsche med. Wchnschr. **81**:1204 (Aug. 10) 1934.

was no other source of vitamin C in the diet, the patient, taking each day 60 mg. orally, showed definite improvement in two days and was considered cured in twelve days, with a gain of 550 Gm. in weight. Brugsch [33] also reported its use in a child 13 months old, with clinical and roentgenographic evidence of scurvy, which was cleared up in three weeks with a dose of 30 mg. a day. He mentioned a similar study by Parsons and Svensgaard. An important factor in these reports is the apparent tolerance of these young infants to cevitamic acid taken by mouth. Kramer [34] showed in 1933 that daily doses of from 20 to 50 mg. for several weeks were well tolerated by infants, including premature infants. In investigating the tolerance to cevitamic acid,[29] it has been found that mice showed no disturbances when given as much as 50 mg. of cevitamic acid a day for twelve weeks. Guinea-pigs tolerated one hundred times the protective dose for five weeks without change.

Böger and Schroeder,[35] after observing the favorable effect of cevitamic acid, parenterally administered, on capillary hemorrhages of C avitaminosis origin, were encouraged to try its use in a variety of other hemorrhagic conditions. They reported first a case of Schönlein-Henoch's purpura, in which they observed a rapid disappearance of the phenomena of increased capillary fragility by the intravenous administration of 100 mg. daily. This patient's condition had not been influenced by the previous use of vitamin C by mouth. This phenomenon will be discussed later. The second patient whom Böger and Schroeder discussed was a man with hemophilia, who had severe intestinal hemorrhages. After the daily administration of 150 mg. of cevitamic acid intravenously for a few days the bleeding ceased. They did not point out that bleeding frequently stops in patients with hemophilia without any therapy. The third case in this series was that of a man aged 60, with acute thrombocytopenic purpura. He had bleeding from the mucous membranes and subcutaneously and very bloody urine and tarry stools. The patient was acutely ill. After receiving 150 mg. of cevitamic acid intravenously for four days, the bleeding ceased and did not recur. The significant findings in the blood were more striking. When the patient was first seen, the platelets were too few to count. Curiously, the bleeding ceased two days before the platelets became plentiful enough to count. There was thereafter a steady increase in number until, after one month of therapy with cevitamic acid (100 mg. daily), the count reached 304,000. During the same time the bleeding time decreased from twelve to one and a half minutes. This case emphasizes a point to be stressed later, namely, that the number of platelets

33. Brugsch, H.: Deutsche med. Wchnschr. **81**:1202 (Aug. 10) 1934.

34. Kramer, E.: Deutsche med. Wchnschr. **59**:1428 (Sept. 15) 1933.

35. Böger, A., and Schroeder, H.: München med. Wchnschr. **81**:1335 (Aug. 24) 1934.

is not the determining factor per se of the clinical course of thrombocytopenic purpura. It is frequently noted that immediately after splenectomy the bleeding stops, although the platelet count does not increase and may even decrease. These authors concluded that it is extremely probable that vitamin C acts on the vessels and that obviously an alteration of the permeability of the walls of the vessels plays an important part in the occurrence of hemorrhages in Werlhof's disease. We feel that such a conclusion cannot reasonably be drawn from one case and that this report can be interpreted only in the light of future findings. These authors reported also an increase in the amount of albumin in the serum with this treatment and expressed the opinion that this may be a factor in stopping the bleeding. The increase they reported was from 5.02 mg. to 6.39 mg. per hundred cubic centimeters. They studied these changes further and reported [36] that both in persons with hemorrhagic conditions and in normal subjects the administration of 100 mg. of cevitamic acid daily resulted in a marked increase of the total amount of protein. This was first noticeable after the third day; the increase was largely confined to the albumin fraction, while the values for globulin and fibrinogen were little changed.

In a recent communication [37] Professor Szent-Györgyi reported favorable results in cases of hemorrhagic nephritis, purpura, pyuria, pyorrhea and agranulocytosis. The dosage used was from 150 to 200 mg. on alternate days.

Before proceeding with a summary of our experience with the use of this drug, we feel that a brief discussion of a test which we have found most useful in evaluating the clinical course of these diseases is in order. For the past five years we have been especially interested in a study of human capillaries [38] and throughout this time have been seeking a satisfactory and simple test of capillary fragility. None thus far has been entirely satisfactory,[39] but we have found the following modifi-

36. Böger, A., and Schroeder, H.: Klin. Wchnschr. **23**:842, 1934.

37. Szent-Györgyi, A.: Personal communication to the authors, Nov. 27, 1934.

38. Duryee, A. W., and Wright, I. S.: Am. J. M. Sc. **185**:664 (May) 1933. Wright, I. S.: The Clinical Value of Human Capillary Studies, J. A. M. A. **101**: 439 (Aug. 5) 1933. Wright, I. S., and Duryee, A. W.: Human Capillaries in Health and in Disease, Arch. Int. Med. **52**:545 (Oct.) 1933. Wright, I. S., and Moffat, D.: The Effects of Tobacco on the Peripheral System, J. A. M. A. **103**: 318 (Aug. 4) 1934.

39. Cutter, Irving and Marquardt, Gilbert: Proc. Soc. Exper. Biol. & Med. **28**:113 (Nov.) 1930. Hess, A. F.: Recent Advances in Knowledge of Scurvy and the Antiscorbutic Vitamin, J. A. M. A. **98**:1429 (April 23) 1932. Dalldorf, G.: A Sensitive Test for Subclinical Scurvy in Man, Am. J. Dis. Child. **46**:794 (Oct.) 1933. Lindberg, A.: Hygiea **95**:10 (Jan. 15) 1933. Göthlin, G. F.: J. Lab. & Clin. Med. **18**:484 (Feb.) 1933. Stocking, R. E.: Arch. Pediat. **50**: 823, 1933. Greene, D.: Evaluation of the Capillary Resistance Test in the Diagnosis of Subclinical Scurvy, J. A. M. A. **103**:4 (July 7) 1934.

cation of the tourniquet test (Rumpel-Leede phenomenon) to be sufficiently standardized to be of great value:

A circle 2.5 cm. in diameter, the upper edge of which is 4 cm. below the crease of the elbow, is drawn on the inner aspect of the forearm. Any skin blemishes within the circle which could possibly be confused with petechiae are marked with ink. The rubber cuff of a mercury blood pressure manometer is then applied as usual around the upper part of the arm and inflated to a pressure midway between the systolic and the diastolic pressure of the patient. This is maintained for fifteen minutes, after which the pressure is released; at the end of five minutes the number of petechiae within the circle is counted with the naked eye. From many observations we believe that an absolutely normal count is rarely above 10, that there is a marginal zone between 10 and 20 and that a count above 20 is definitely abnormal. We have attempted to standardize this test so that all workers might be able to discuss their results with mutual understanding and have tried at the same time to keep it free from a need for special apparatus, so that it might have universal use. We found the zone of the crease of the elbow to be tremendously variable in the numbers of petechiae produced, without corresponding significance. There does appear to be a downward gradient below the elbow, and 4 cm. was taken as an arbitrary distance, far enough from the irregularities of the crease of the elbow. Two and five-tenths centimeters for the diameter is also arbitrary, being sufficient to encompass a fair-sized area but not too large to permit of ease in counting the petechiae. As a further refinement, two or three circles of this size might be drawn at the same level and the average count of the two or three taken. The cuff pressure suggested might well be criticized, but we aimed merely to arrive at a pressure which guaranteed a greatly increased capillary pressure with no venous escape. We deprecate the use of a magnifying glass to count the petechiae as merely complicating the situation and not adding practically to the information.

In certain patients, because of discomfort or excessive subcutaneous hemorrhages, it may be desirable to use seven and a half minutes instead of fifteen minutes as the standard. All further readings taken on the same person should be taken with the modified time. This test may be done every four days on alternate arms (thus giving the capillaries of each arm from seven to eight days to heal).

We readily admit that other conditions in addition to scurvy may produce or increase the number of petechiae and also that other factors, such as season, race and edema and, rarely, the menses, may cause fluctuations. This test is, nevertheless, as we shall demonstrate later in this paper, a valuable aid, not only in the study of these conditions but also as a guide to therapeutic results.

Another problem which needs clarification at this point is the incidence of vitamin C deficiency in adults. It has become increasingly evident that in spite of the publicity given vitamins and the available supply of citrus fruits there are many cases of C avitaminosis, the milder of which are usually unrecognized. In the course of nine months we have seen twenty patients for whom a diagnosis of vitamin C deficiency could be reasonably established. The chief causes have been dietary—diets conditioned by poverty and diets prescribed by the medical pro-

fession or chosen by the patient, either because of preference or because of adherence to some food faddism. We have seen even severe evidences of scurvy which have developed as a result of diets prescribed for ulcer, colitis and urticaria and which have been unrecognized by the attending physician. It must be acknowledged that many of these cases represent a mixed avitaminosis and also that there are many more which are "subclinical." This subject was well reviewed by Mettier, Minot and Townsend in 1930.[40]

Another much rarer group of patients appears to be unable to utilize a vitamin intake which should be fully adequate. Although in principle this possibility was suggested by Fenwick[41] and others, Castle and Locke[42] were the first to demonstrate clearly that irrespective of the adequacy of the diet certain abnormalities in the gastric secretion might condition a state of dietary deficiency. Strauss[43] discussed this problem in relation to certain deficiencies in 1934. Jackson[44] demonstrated that vitamin A, if it was ingested at approximately the same time as liquid petrolatum, could be carried through the intestinal tract without absorption. That vitamin C may be unused, though taken in adequate amounts, is suggested by several interesting observations; the first is that a scorbutic-like syndrome may develop while a person is taking large amounts of citrus fruit (from two to three oranges a day), and the second, that certain workers[27] noted that some scorbutic patients failed to respond to fruit juice or cevitamic acid given by mouth but responded and recovered when given cevitamic acid intravenously. We have confirmed this finding and have induced a relapse by placing several such patients on a regimen of vitamin C by mouth; they have been recured with cevitamic acid administered intravenously. The mechanism producing such a phenomenon certainly is not understood, but the following possibilities suggest themselves: (*a*) anacidity or imbalance of the gastric secretion; (*b*) bacterial destruction of the vitamin in the upper part of the gastro-intestinal tract; (*c*) inflammatory changes of the intestinal mucous membrane; (*d*) accelerated action of the intestinal tract due to diarrhea of a variety of causes, including laxatives; (*e*) the use of oily laxatives which may hold the vitamin, as already demonstrated with vitamin A, and finally (*f*) changes which may take place after absorption but which render the vitamin inert.

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40. Mettier, S. R.; Minot, G. R., and Townsend, W. C.: Scurvy in Adults; Especially Effect of Food Rich in Vitamin C on Blood Formation, J. A. M. A. **95**:1089 (Oct. 11) 1930.

41. Fenwick, Samuel: On Atrophy of the Stomach and on the Nervous Affections of the Digestive Organs, London, J. & A. Churchill, 1880.

42. Castle, W. B., and Locke, E. A.: J. Clin. Investigation **6**:2 (Aug.) 1928.

43. Strauss, M. B.: The Rôle of the Gastro-Intestinal Tract in Conditioning Deficiency Disease, J. A. M. A. **103**:1 (July 7) 1934.

44. Jackson, R. W.: J. Nutrition **4**:171 (July) 1931; ibid. **7**:607 (June) 1934.

As criteria of "subclinical" or early scurvy, we used the history of a diet poor in vitamin C taken over a protracted period of time, a definite increase in capillary fragility on several checked tests and a response by a decrease in capillary fragility to within the normal range (0-10) on exactly the same regimen with the single addition of cevitamic acid.[45]

VITAMIN C DEFICIENCY

The first series of cases which we report is grouped under the heading of vitamin C deficiency. Three of these cases have been briefly reported elsewhere.[46]

Chart 1 shows graphically the effect of vitamin C (cevitamic acid), whether taken by mouth or intravenously, on the capillary fragility. Without exception it was possible to reduce the number of petechiae to less than 15, and in only one patient (F. K.), whom we could not follow longer, was the final figure above 10, the figure we consider to represent the upper limit of normal. Patient R. B. is of especial interest, since her capillary fragility improved from 63 to 14; then, when she once more was on a diet very low in vitamin C, because of poverty, the capillary fragility remounted to 70. Once more it was possible by using 0.09 Gm. daily by mouth to reduce the number of petechiae from 70 to 10 in two weeks. Patients E and N also received other concentrated vitamins to supplement treatment, so their curves may be considered of less value. We have not noted, however, that other vitamins influence capillary fragility.

Each case history will be discussed separately.

Case 1.—W. J., a male nurse, aged 52, was first seen on May 20, 1934. He had had a distaste for fruits all his life and had been on a diet deficient in vitamin C for many years. According to his own statement, he did not believe that he "took one piece of fruit a year." For the previous three months, because of a condition diagnosed as "colitis and possible malignancy," he had been on a diet consisting of cream, eggs, rice and soda crackers with an occasional piece of breast of chicken. He had been taking tincture of belladonna, 15 drops three times a day. He smoked from eight to ten pipefuls of tobacco a day. At this time his complaints were loss of weight, nasal hemorrhages, bleeding gums, bleeding from the rectum, marked discomfort with a sense of a mass in the rectum and extreme weakness, which made it difficult for him to walk even a very short distance.

Physical examination revealed the following: The gums were soft and bleeding and the teeth very loose. There were perifollicular cutaneous hemorrhages on both legs about the knee and on the left shoulder anteriorly; there were multiple subcutaneous hemorrhagic areas, averaging 2.5 cm. in diameter, over the tibias.

The capillary fragility test showed 90 petechiae. The blood pressure was 110 systolic and 70 diastolic. The blood count revealed: white cells, 7,400; red cells,

45. All cevitamic acid used in this study was supplied by Merck Co., Inc.

46. Wright, I. S.: Proc. Soc. Exper. Biol. & Med. **32**:475 (Dec.) 1934.

4,600,000; hemoglobin, 106 per cent (Sahli), and platelets, 190,000. The bleeding time was four minutes, and the clotting time, four minutes. The differential count revealed: polymorphonuclears, 69 per cent; small lymphocytes, 13 per cent; large lymphocytes, 15 per cent; eosinophils, 1 per cent, and basophils, 2 per cent.

May 23: The patient weighed 112 pounds (50.81 Kg.). He was instructed to maintain exactly the same diet previously described (a diet low in vitamin C) and was given crystalline vitamin C, 0.02 Gm. orally, three times a day.

June 1: According to the patient, the gums were no longer bleeding, the teeth were firmer, there were no new perifollicular or subcutaneous hemorrhages and there had been a diminution of nasal and rectal bleeding. The capillary fragility test showed 90 petechiae (no change). The patient was instructed to continue the crystalline vitamin C, 0.06 Gm. a day orally.

June 7: The patient reported a great general improvement and a marked increase in strength. He said that he had had no further nasal hemorrhages or

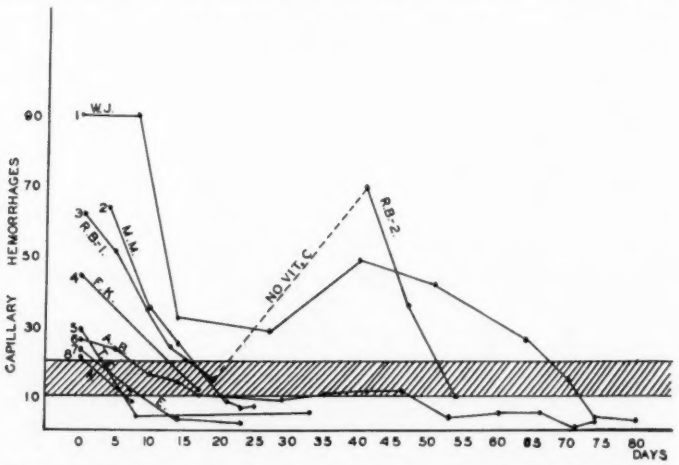

Chart 1.—The effect of cevitamic acid on the capillary fragility in eight cases of vitamin C deficiency.

purpuric spots and had had on an average only one bloody stool each day instead of continuous bloody diarrhea. The capillary fragility test showed 32 petechiae.

June 19: The improvement continued. The gums appeared more normal. The teeth were firmer. The capillary fragility test showed 29 petechiae. The weight had increased to 129½ pounds (58.7 Kg.), and there was a great increase in strength.

July 3: The improvement continued. Rectal bleeding was rarely noticed. The gums were normal and did not bleed. The teeth were firm in the sockets. The weight was 132½ pounds (60.1 Kg.). The capillary fragility test showed an increase to 49 petechiae. Up to this point the patient had continued taking 0.06 Gm. of cevitamic acid a day. At this time he was instructed to take 0.1 Gm. daily, in view of the increase in the number of petechiae.

July 13: He continued to feel stronger, with very rare rectal bleeding. The teeth were absolutely solid, and the patient reported that he believed that he would

be able to chew tough foods, if permitted. He weighed 134 pounds (60.8 Kg.). The capillary fragility test showed 42 petechiae. He was then instructed to take 0.09 Gm. of cevitamic acid orally each day and to continue on the diet low in vitamin C.

July 27: Continued improvement was reported. Rare small spots of blood were noted in the stool. No bleeding was seen elsewhere. The weight was 135½ pounds (61.4 Kg.). The capillary fragility test showed 26 petechiae.

August 4: The patient reported that he considered himself in perfect health and that he "couldn't feel better." Rare, slight streaks of blood or mucus were seen in the stool. The weight was 139 pounds (63 Kg.). The capillary fragility test showed 15 petechiae. The patient had been at work for the previous week, which necessitated his walking from 8 to 10 miles a day, and he felt perfectly capable of performing this exercise without undue fatigue. The dosage of cevitamic acid was reduced to 0.06 Gm. orally each day.

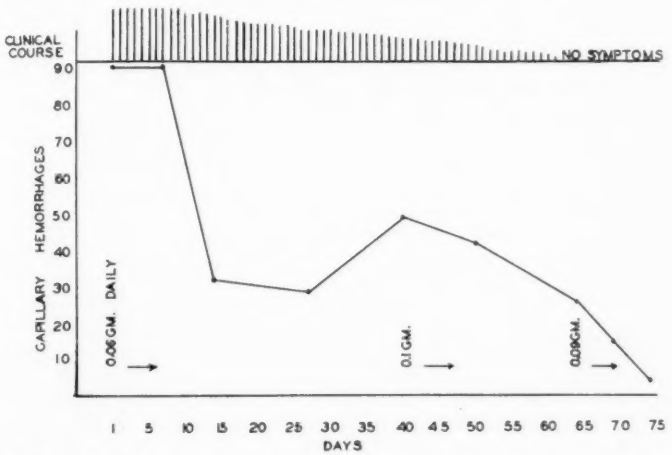

Chart 2.—The effect of cevitamic acid administered orally on the capillary fragility of patient W. J.

August 15: The patient's complaints and the results of the physical examination were negative as far as any evidence of the scorbutic condition could be determined. He reported no mucus with his stools. The weight was 142 pounds (64.4 Kg.). The capillary fragility test showed 4 petechiae. The patient was then placed on a general diet high in vitamins and was discharged.

NOTE.—Throughout the study of this case the capillary fragility tests were done with the Baumanometer blood pressure machine at the half-way mark between the diastolic and the systolic pressure for fifteen minutes.

Comment.—The clinical course in this case is interesting and significant. Moderate scurvy developed as a result of the patient's native dislike for fruits containing vitamin C. As we review the clinical course under treatment, it seems probable that the hemorrhages from the bowels were severe manifestations of the scorbutic syndrome. The

medical attendant, failing to recognize this, treated the patient for a hemorrhagic form of colitis and placed him on a bland diet poor in vitamin C. On this regimen, the scorbutic syndrome, associated with a marked loss of weight and increased weakness, continued to develop. The fact that merely by adding crystalline vitamin C to the diet which had accentuated the pathologic condition we were able to produce a complete reversal of symptoms, with a steadily progressive improvement in each aspect, was particularly interesting. This improvement included complete cessation of hemorrhage and its accompanying discomfort, decrease in capillary fragility to well within normal limits, a gain in weight from 112 to 142 pounds (50.8 to 64.4 Kg.), and such a gain in strength that instead of being barely able to walk he was enabled to carry on a daily occupation which necessitated from 8 to 10 miles of walking.

CASE 2.—M. M., aged 57, a Polish Jew, had lived for years on a depleted diet, which for more than one year before his admission to the Bellevue Hospital (April 12, 1934) had contained practically no foods which could be considered sources of vitamin C (fresh fruits, fresh green vegetables, liver, etc). One year before he had been confined to another hospital with pains in his legs. For three weeks before admission he had felt "sick all over," with generalized aching. He had had no food for four days preceding admission. On physical examination he presented the classic picture of adult scurvy, with the following positive findings: poor nutrition, disorientation, bleeding with very marked erosion of the gums, large subcutaneous hemorrhages in the areas of the left thigh, left knee and both legs (these areas varied in size up to about 6 square cm.), multiple small perifollicular hemorrhages scattered over the extremities and extreme tenderness over both legs and over the humerus, radius and ulna of both arms. In addition, he showed moderate cardiac enlargement, generalized arteriosclerosis, early clubbing of his fingers (unexplained) and a large scrotal hernia on the right side.

April 13: On the basis of the diagnosis of scurvy, the patient was placed on a diet high in caloric and vitamin content, with the forcing of citrus fruit juices, of which he received from 180 to 300 cc. a day. A moderate secondary anemia was present, which improved with vitamin C therapy.

The Wassermann and van den Bergh tests and urinalysis gave negative results. Throughout the patient's stay in the hospital his pulse, temperature and respiratory rate showed no significant variations. His blood pressure was 170 systolic and 100 diastolic and later 140 systolic and 84 diastolic. Roentgenograms of the extremities did not show definite subperiosteal hemorrhages.

April 17: After four days on the diet high in vitamins, the general condition was much improved. There were no new hemorrhagic areas, and the gums bled less readily. The patient was slightly more alert mentally.

April 24: On the eleventh day of treatment his progress had been steady but slow. No new hemorrhages had occurred; the gums were less tender, but mentally the patient was semirational, with periods of lucidity. His blood pressure was 130 systolic and 80 diastolic. The capillary fragility test made at this time, after eleven days of a diet high in vitamin C, showed 39 petechiae. The patient was then placed on a diet free from vitamin C, consisting of cereals and breadstuffs.

April 28: After four days on this restricted diet he was definitely worse. His gums bled spontaneously, and he was practically comatose, with periods of irrationality. The capillary fragility test produced 64 petechiae, corresponding to the definite progression of the scorbutic syndrome. He was then kept on the scurvy-producing diet, with the addition of cevitamic acid, 0.02 Gm. orally three times a day.

May 4: In seven days he showed a remarkable general improvement. His mental condition was markedly cleared. He held a rational conversation and expressed a desire to sit up. His gums still bled on pressure, but he had had no new hemorrhages, and all tenderness had disappeared. The capillary test showed 35 petechiae.

May 8: On the twelfth day of the cevitamic acid regimen the patient was absolutely clear mentally (although his intelligence quotient was low). He held

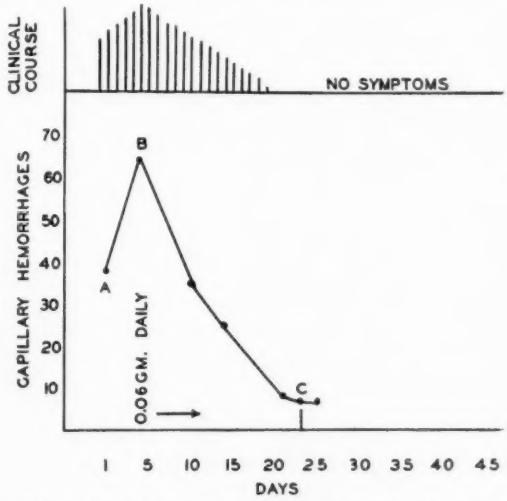

Chart 3.—The effect of cevitamic acid administered orally on the capillary fragility of patient M. M.

long conversations in English and Polish. He was allowed to sit up and desired to go home. His gums appeared secondarily infected, and examination revealed organisms resembling Vincent's. The capillary fragility test produced 25 petechiae.

May 14: On the eighteenth day the capillary fragility test produced 8 petechiae, which is considered to be within the normal limits. The patient had been out of bed each day.

May 16: On the twentieth day a recheck showed 7 petechiae. The patient was then placed on a regular, well balanced diet with a high vitamin C content.

Comment.—This case is of especial interest in that the scorbutic syndrome was definitely improved with the ingestion of citrus fruits, made worse by a diet poor in vitamin C and cured by the addition of only cevitamic acid to the diet which was responsible for the relapse.

The results of the capillary fragility test followed the clinical course very closely.

CASE 3.—R. B., a woman aged 52, was seen with the complaint of weakness and pain and swelling of both ankles, especially the right, of three weeks' duration. Bilateral salpingectomy had been performed twenty years before. One and a half years before glaucoma developed over the eyes. Because of poverty, she had been on a markedly depleted diet for the year immediately preceding this examination. During this time she had taken very little food containing vitamin C and during the last month had had no appreciable amounts of vitamin C.

Physical examination showed a fairly well developed but chronically ill woman. Her few remaining teeth were carious. Her gums were spongy, oozed blood slightly and bled easily on pressure. The abdomen was normal except for a suprapubic scar from an old salpingectomy. Abdominal reflexes were not elicited. There was edema of both ankles, especially the right. The knee jerks were not elicited. The blood pressure was 180 systolic and 120 diastolic.

The Wassermann reaction was negative. The urine was normal, and the platelets numbered 190,000. The capillary fragility test showed 61 petechiae in fifteen minutes.

The patient was given 0.09 Gm. of cevitamic acid orally a day. Her general condition improved markedly. The edema cleared up. The capillary fragility was markedly decreased, as noted on chart 1. On the twenty-sixth day there were only 14 petechiae seen after a fifteen minute test.

The patient then left the hospital and once more was on a very depleted diet, with an inadequate supply of vitamins, because of poverty. Twenty-two days later she returned to the hospital after having had a recurrence of her weakness and edema. The capillary fragility test once more showed an increase to 70 petechiae in fifteen minutes. Although we were unable to improve the patient's general diet appreciably, she was given a supply of cevitamic acid which enabled her to take 0.12 Gm. orally a day. After seven days the capillary fragility test showed 36 petechiae, and after another seven days, 10 petechiae. The edema had cleared up completely.

Comment.—This case seems to be a true instance of malnutrition in which lack of vitamin C was one of the major factors. It is recognized that in all cases of malnutrition there is probably a mixed avitaminosis, but this patient responded very quickly and satisfactorily to the addition of large amounts of vitamin C alone. The fact that when the patient abstained from vitamin C she had a recurrence of her condition and that it once more cleared up when the vitamin was used would seem to establish beyond question the value of cevitamic acid in her case.

CASE 4.—F. K., a woman aged 48, was first seen on June 27, 1934. Her chief complaint was innumerable subcutaneous hemorrhages with marked epistaxis at night and hematuria. Careful inquiry into her dietary history revealed that for many years she had had an aversion to citrus fruits and other sources of vitamin C.

Physical examination gave essentially negative results, except for a questionable mass and slight tenderness over the left flank and costovertebral region. Complete studies of the blood, including red cell count, white cell count, differential count and determinations of hemoglobin, bleeding and clotting time, cell fragility

and coagulation time, were made and checked several times, the results being within normal limits. The capillary fragility test, however, revealed 43 petechiae after ten minutes, the patient being unable to continue the test longer because of discomfort.

The patient was placed on a regimen of 0.06 Gm. of cevitamic acid by mouth daily for two weeks and then 0.09 Gm. daily for three days. At the end of that period the capillary fragility test revealed 11 petechiae in ten minutes. During this time studies of the urinary tract indicated a renal tuberculosis on the left side, and on July 12 nephrectomy was performed. Before the operation the nasal hemorrhages had ceased and only an occasional purpuric spot was noted. The patient was discharged thirteen days later, on July 25. No cevitamic acid was given from July 12 to July 20, following immediate operative convalescence. After that period she was given 0.06 Gm. orally per day. No purpuric spots or hemorrhages were noted after the operation.

The patient did not return for further follow-up study.

Comment.—The question may well be raised as to whether this case should be classified as one of early vitamin C deficiency produced by lack of intake over a prolonged period of time, whether the patient represents one of those persons who, in addition, because of the presence of an infection, appear to drain their vitamin C resources more rapidly or whether the case be classified as one of nonthrombocytopenic purpura associated with a low grade chronic infection. In favor of the scorbutic diagnosis is the fact that both the clinical course and the capillary fragility improved considerably before operation with the administration of cevitamic acid.

Case 5.—T. C., a woman aged 22, was first seen on July 13, 1934. Her chief complaint was severe pain in the midepigastrium, especially from two to three hours after eating. It was formerly relieved by alkalis and food but not relieved by any medication during two weeks preceding examination. Four days before admission the patient had a severe gastric hemorrhage. Four years previous to this time she had symptoms resembling those of a peptic ulcer. Following inadequate study a surgeon did a partial gastrectomy, but the pathologic examination of the tissue revealed only acute gastritis. Ever since then the patient had been on a diet practically free from fruit and fresh uncooked vegetables. For the first six months following the operation she had had no symptoms, but since that time she had had the symptoms typical of a duodenal ulcer. Six months before admission she had her first gastric hemorrhage.

After being placed on a Sippy diet, her symptoms diminished but did not disappear, and, as noted previously, she had another severe hemorrhage just previous to admission. The capillary fragility test on admission showed 27 petechiae. She was placed on a Sippy diet with alkalis and was given 0.06 Gm. of cevitamic acid daily by mouth. On the fifth day the capillary fragility test showed 4 petechiae, and twenty-five days later the count had not risen above the level of 6 petechiae.

Comment.—It is not our purpose to discuss in detail the diagnosis and treatment of the marginal ulcer which was revealed in the roentgenogram of this patient. From the point of view of the problem we are discussing, however, several points are very important. One is the

evident need for the inclusion of an adequate source of vitamin C in the diets of patients who are on modified diets for ulcer over a long period of time. The very stringency of these diets, particularly in reference to foods containing vitamin C, would tend to increase the likelihood of increased capillary fragility and hence may predispose to free bleeding from the ulcers. The second point of interest is that this patient was able to take cevitamic acid within a few days after having had a hemorrhage without any signs of gastric irritation. In fact, she stated that on repeated tests the cevitamic acid appeared to relieve her discomfort more satisfactorily than the alkali powders prescribed. The third point of interest is a definite improvement in capillary fragility, as evidenced by the use of capillary fragility tests.

CASE 6.—A. B., a woman aged 57, was first seen on Sept. 10, 1934. The chief complaints at the time of admission were extreme general weakness, vomiting, pain and weakness of the right side of the face and multiple large purpuric spots (from 2 to 5 cm. in diameter) scattered over the left arm, the left hip and both legs, of one week's duration.

Appendectomy was performed twenty-seven years previously. Intermittent pain in the epigastrium was diagnosed twelve years previously on roentgen examination as a duodenal stricture. The patient had never vomited blood, nor had she had tarry stools. Cholecystectomy was performed twelve years previously. Thyroidectomy was performed eight years previously, at which time the parathyroid glands were partially removed because of enlargement; the exact pathologic process of this enlargement has not been definitely established. Four years previously the patient fell, fracturing one vertebra. Five months previously she fell, fracturing both humeri. During the six years previous to this time she had scattered over the trunk and extremities a constant succession of large purpuric spots, each of which had taken from five to six weeks to disappear. She had always taken large amounts of citrus fruits and fruit juices. The weight was 135 pounds (61.2 Kg.).

On physical examination the patient appeared chronically ill, with moderate pallor. There was palsy of the right side of the face, with a distribution typical of Bell's palsy. There was a thyroidectomy scar. A rough systolic murmur was heard over the apex of the heart, transmitted toward the base. The abdomen was normal except for scars following an upper right rectus and a McBurney incision. The cervix was slightly eroded and bilaterally lacerated.

Rectal examination revealed internal hemorrhoids but no bleeding. Examination of the skin showed large purpuric spots, ranging from 2 to 5 cm. in diameter, scattered over the left arm, the left hip and both legs. The blood pressure was 162 systolic and 78 diastolic. Laboratory studies showed the following: blood cultures, negative; basal metabolism, plus 11.7 per cent; electrocardiographic tracing, negative. The results of gastric analysis follow:

	Hydrochloric Acid		
	Free	Combined	Total
Fasting content	0	19	19
½ hour (after 75 cc. of 7 per cent. alcohol)	16	33	49
1 hour	23	13	36

Lactic acid—0
Occult blood—0

The blood count revealed: red blood cells, 4,230,000; hemoglobin, 86 per cent; white blood cells, 5,700; polymorphonuclears, 68 per cent; band forms, 7 per cent; leukocytes, 22 per cent, and mononuclears, 22 per cent. The Wassermann reaction of the blood was negative. The red cells showed slight variation in size and shape. There was moderate polychromatophilia.

On September 10 the platelet count was 90,000. The capillary fragility test showed 26 petechiae in seven and one-half minutes. The bleeding time was from one and one-half to two minutes; the coagulation time, from four and one-half to five minutes.

The patient was given cevitamic acid intravenously. The first dose was 0.05 Gm., and thereafter she was given a daily injection of 0.1 Gm. Beginning with the fourth day the patient reported feeling much stronger and generally better. The purpuric spots had almost entirely cleared up, and no new ones were noted.

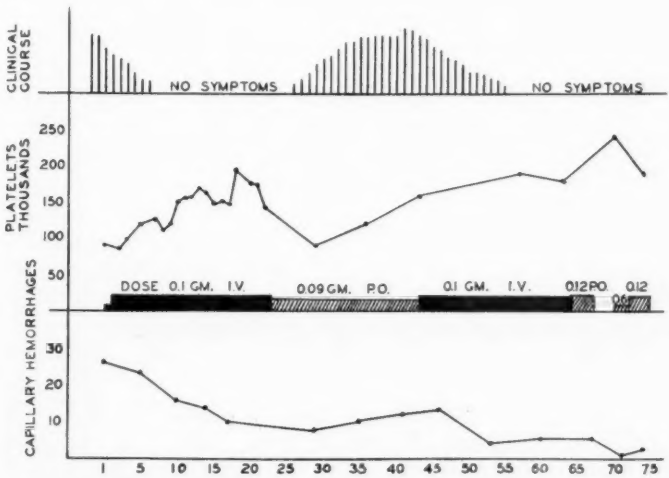

Chart 4.—The effect of cevitamic acid on patient A. B.

Seven days after the first injection the patient was discharged from the hospital. She claimed at this time that she felt well enough to return to her work. She continued to receive daily injections of cevitamic acid intravenously. Chart 4 shows the changes in the platelet count and capillary fragility which took place over a period of seventy-five days of observation.

After the twentieth injection, in order to simplify treatment, the patient was given cevitamic acid orally, 0.09 Gm. daily. At that time, she was feeling very well and had had no new purpuric spots, but shortly after she began to feel less strong, and new purpuric spots appeared. This became more pronounced, until on the sixteenth day of oral administration was begun she fainted and was readmitted to the hospital. Her condition was essentially the same as it had been on the previous admission, except that the palsy on the right side of the face had entirely cleared up. Three or four purpuric spots, from 1 to 2 cm. in diameter, were seen above the right ankle and the right eyelid.

On the sixth day after admission she was again placed on a regimen of intravenous medication with cevitamic acid, 0.1 Gm. per day. During this admission roentgenograms of the gastro-intestinal tract showed no organic pathologic process. The basal metabolism was plus 10.9 per cent. The red blood cells numbered 4,200,000, and the hemoglobin content was 76 per cent. The white blood cells numbered 6,600, with a normal differential count. The urine was normal. The calcium content of the blood was 10 mg. per hundred cubic centimeters; the phosphorus content, 4.1 mg. The blood pressure was 160 systolic and 70 diastolic.

The patient showed marked improvement in strength; there was no recurrence of purpuric spots on the intravenous administration of cevitamic acid. She was discharged from the hospital after seventeen daily injections.

She continued to receive 0.1 Gm. per day intravenously and felt very much stronger for ten days. At the end of this period she was given 0.12 Gm. orally per day (4 tablets, 0.01 Gm. per tablet, three times a day). After fourteen days on this regimen she reported that she had continued to improve, that she had had no purpuric spots, that she had gained in weight from 135 to 152 pounds (61.2 to 68.9 Kg.), that her appetite had returned and that she no longer suffered from insomnia, which had been a chronic complaint for a long time. (Since the completion of this study the patient has had three episodes, each characterized by collapse and the appearance of purpuric spots, subsequent to the use of cevitamic acid by mouth. Intravenously administered cevitamic acid has produced marked improvement following each of these attacks.)

Comment.—This case presents a syndrome which is difficult to classify. The platelet count was definitely lowered, and there was evidence of subcutaneous bleeding. These facts might lead one to believe that the patient was suffering from mild thrombocytopenic purpura. The history of taking large amounts of citrus fruits would tend to influence the diagnosis away from scurvy, and yet we have seen a number of patients who apparently cannot utilize vitamins, even when they are adequately taken. This has been stressed recently by several authors. The fact that this patient responded so well to intravenous medication and rather poorly to cevitamic acid by mouth during the first attempt would lead one to believe that she might fall within that group. This has been further confirmed by the fact that she has had three subsequent episodes characterized by the onset of purpuric spots and great weakness. Each of these attacks has cleared up with the use of cevitamic acid intravenously. The patient is at present recuperating slowly from the shock of a Colles fracture. It should be noted in the report on the gastric analysis that free hydrochloric acid was absent until the alcohol was given. This has been reported as frequently associated with the group of persons who cannot utilize vitamin C taken by mouth.

We shall not attempt an explanation of the increased platelet count associated with the administration of cevitamic acid. It is noteworthy that it reached high levels on several occasions (191,000 and 240,000) but failed to remain there, although the administration of cevitamic acid was continued. On the other hand, it is clear that the average daily

level was much higher from the ninth injection throughout the remaining sixty-six days. The result of the capillary fragility test was not markedly high at the beginning (26 petechiae in seven minutes), although if the patient could have tolerated the discomfort of the Baumanometer cuff for fifteen minutes it would have been higher. The number of petechiae has decreased with successive readings and has been well within normal during the past month.

CASE 7.—E., a widow aged 63, a German, until eight or nine years before this examination had been free from any illness of importance which might have had a bearing on the present problem. She became disturbed about an unhappy marriage of one of her daughters, lost her appetite and then started to drink immoderately, thus forming a habit which further decreased her food intake.

About ten years previously she had remarried, marrying a man who demanded a great deal of domestic attention, i. e., as to clothing, meals, etc., and who ate only heavy, hearty food, such as corned beef and cabbage, sauerkraut, potatoes, etc. This resulted in her eating small amounts of vegetables, fruit, milk, etc. Six years ago she began to feel weak, and five years ago she had a massive rectal hemorrhage. Her physician diagnosed her condition as ulceration of the bowel, placed her on a diet of milk, cream and soda crackers, and prescribed ½ grain (0.032 Gm.) of morphine to be taken at any time for pain and hemorrhage. This continued until the spring of 1934, when her physician died, and his nephew, who assumed his practice, ordered her to discontinue the morphine and replace it with alcohol. She continued to take camphorated tincture of opium, which she obtained from drug stores, but, in addition, began to drink enough alcohol to result in frequent intoxication. Her abdominal pain became worse, with colicky paroxysms. Her stools were mucopurulent and bloody. She could not eat regular food or take fruit juices because of gastro-intestinal distress. A sore tongue, bleeding, swollen, painful gums and loose teeth developed. She bruised very easily. The backs of her hands became hardened and rough.

The significant physical findings were as follows: obesity; disorientation; constricted pupils (morphine); foul breath; loose teeth; swollen, bleeding, dirty gums; a red, swollen, smooth tongue; large purpuric spots about the left shoulder joint, the left thigh and scattered elsewhere over the body and rough, thickened, brownish, discolored skin on the dorsa of the hands. The data from laboratory tests is shown in the table.

Results of Laboratory Tests

Date	Capillary Fragility Test	Platelets	Red Blood Cells	Color Index
9/19/34	19			
9/24/34	Patient put on 0.06 Gm. of cevitamic acid orally daily			
9/24/34	23	60,000	3,750,000	0.8
10/ 1/34	12	140,000	4,230,000	0.8
10/ 8/34	4	175,000	4,720,000	0.85
11/17/34	2	220,000	4,610,000	0.9

Unfortunately, from the point of view of controlled observation, this patient received large amounts of other vitamins and fruit juices also during treatment. The consumption of alcohol was stopped. The patient was unable to take regular foods and especially fruit juices at first, because of resultant discomfort, but during this time she did take cevitamic acid. It seemed to relieve the pain (so

she claimed), and she believed that it was given for that purpose. (Note case 5 in which similar results are reported.) After seven weeks on this regimen the patient appeared to be in perfect health, walking and talking spiritedly, with no symptoms referable to the gastro-intestinal tract and with an excellent appetite.

Comment.—This case probably represents another example in which scurvy was diagnosed as ulcerative colitis and made much worse by the dietary regimen ordered by the physician. The capillary fragility test and platelet count showed curves which followed closely the clinical improvement, and they became normal when cure was effected.

It cannot be claimed that cevitamic acid is solely responsible for the cure in this instance, but it was important that it could be given by mouth before the patient could tolerate fruit juices. It may be of no significance, but it should be noted that the patient in case 5 and this patient both spontaneously stated that the cevitamic acid seemed definitely to relieve the pain in the gastro-intestinal region.

CASE 8.—N., a trained nurse, aged 45, for two years had been on a severely restricted diet on account of a cutaneous condition. Review of this diet at once raised doubt as to its sufficiency. Physical examination suggested a mild scorbutic state because of the condition of the gums and the presence of black and blue spots. The capillary fragility test showed 21 petechiae in fifteen minutes. One week of 0.06 Gm. of cevitamic acid daily by mouth and a diet high in vitamins brought the count down to 9. The patient felt so much better that she stopped coming because of distance and cost of travel.

Comment.—The report of this case is included to record another instance of the production of mild scurvy as a result of a therapeutic diet, the tolerance to cevitamic acid and the marked improvement in the capillary fragility and the clinical picture following its use with other vitamins.

It should be noted that we have not found that the use of other vitamins without vitamin C will affect the capillary fragility.

Twelve additional patients with marked scurvy have been promptly cured by the addition of crystalline vitamin C to their previous scurvy-producing diets. This brings this series to a total of twenty.

PURPURA

The next group of patients to be considered consists of those whose condition is included under the heading of "Purpura." This series is admittedly too small for general conclusions to be drawn from it, but the individual case studies are instructive. As may be noted from a study of the histories, although large doses of cevitamic acid were given intravenously, we had no evidence of a favorable effect on the clinical course, the capillary fragility or the laboratory studies in any of these patients. We might, however, if we had not continued our observations

of patient M. G. over a protracted period of time under careful control, have drawn an erroneous conclusion in this regard.

CASE 1.—M. G., a woman aged 45, had had bleeding gums and nasal bleeding for two years. Many purpuric spots and showers of petechiae had been present for three years. This tendency to bleed had been much more marked during the two months preceding examination, with the patient bleeding very freely from the gums, the nose and during menstrual periods. The dietary history revealed that she had been on a diet very low in vitamin C because of poverty and had had only an occasional piece (one in two to three months) of citrus fruit.

Physical examination revealed frank bleeding from the nose and gums, a large number of purpuric spots scattered over the entire body and bleeding from the cervix.

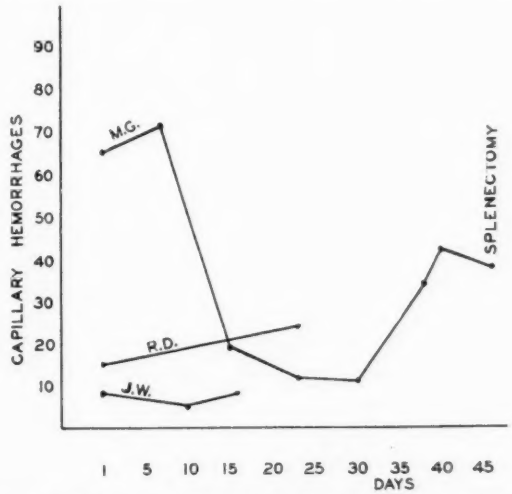

Chart 5.—The effect of cevitamic acid on the capillary fragility in three cases of thrombocytopenic purpura.

Oct. 24, 1934: The capillary fragility test showed 65 petechiae after seven and a half minutes. The platelet count was 60,000. The patient was placed on cevitamic acid, 0.09 Gm. daily by mouth. The capillary fragility tests, platelet counts and clinical course are graphically represented in chart 6.

October 30: Other laboratory studies gave the following results: red blood cells, 3,480,000; hemoglobin, 36 per cent; reticulocytes, 3.8 per cent; white blood cells, 8,500; polymorphonuclears, 50 per cent (band forms, 5 per cent); lymphocytes, 40 per cent; mononuclears, 3 per cent; eosinophils, 2 per cent; clotting time, forty-five minutes, and blood type, no. 2 (Jansky).

November 10: The laboratory examination on this date revealed 2,800,000 red blood cells and 35 per cent hemoglobin. The Wassermann reaction of the blood was negative, and repeated examinations of the urine gave negative results. The average blood pressure was 140 systolic and 90 diastolic. The average temperature during the patient's stay in the hospital was normal. The average pulse rate was 90.

The patient was kept under observation in the hospital for forty-five days. The week preceding admission she received 0.09 Gm. of cevitamic acid a day by mouth. During her stay in the hospital she received 0.1 Gm. intravenously daily, with the exception noted on chart 6. The patient was considered throughout her stay as having thrombocytopenic purpura haemorrhagica idiopathica.

We were anxious to detemine whether cevitamic acid would have any effect on the course of her condition. At first there appeared to be marked improvement. The purpuric spots disappeared, the bleeding stopped from both the nose and the mouth and the capillary fragility test showed a marked decrease in the number of petechiae. Platelets, however, showed no definite changes which could be associated with these evidences of improvement, the count never rising above 90,000. It should be pointed out that while the patient did not receive a diet high in vitamin except for vitamin C, she was leading a much more protected life in bed

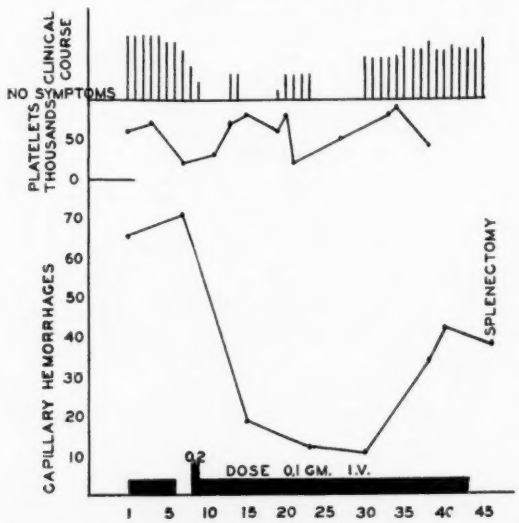

Chart 6.—The effect of cevitamic acid on patient M. G.

in the hospital ward than she had been at home, where she had the care of four young children. If we had stopped our experiment at the end of four weeks we might have been inclined to conclude that she was definitely improved as a result of the use of cevitamic acid. The value of continued observation is, however, forcibly demonstrated, for it is well known that this type of patient is subject to remissions, and on the thirtieth day she began to suffer from a relapse. From that time on bleeding from the gums, nose and cervix and the subcutaneous bleeding gradually increased. The blood studies at this time showed the following: red blood cells, 4,080,000; hemoglobin, 54 per cent; color index, 0.66; white blood cells, 6,800; polymorphonuclears, 54 per cent (bands, 5 per cent); lymphocytes, 35 per cent; monocytes, 5 per cent, and basophils, 1 per cent. A smear showed hypochromia, polychromatophilia, anisocytosis, poikilocytosis and occasional stippled red blood cells, but no nucleated red blood cells. The coagulation time (Howell) was twelve minutes; the clotting time, nine and a half minutes; the bleeding time, approximately one hour. No clot retraction occurred in five days.

The relapse occurred while the patient was receiving 0.1 Gm. of cevitamic acid intravenously daily. On the forty-sixth day she was subjected to a splenectomy. Unfortunately, bronchopneumonia developed and she died.

CASE 2.—R. D., a boy aged 2 years and 11 months, was first seen on Nov. 14, 1934, ten days preceding admission to the hospital. It was noticed that following slight trauma large ecchymotic spots appeared at the point of impact. These contrasted with the previous history of the child, which showed that rather severe injury resulted in very slight if any discoloration of the skin. There was no family history of bleeders. Physical examination gave negative results, except for scattered purpuric spots over the body and extremities. The platelet count, taken daily throughout his stay (three weeks), ranged between 110,000 and 40,000. He was given cevitamic acid intravenously, 0.1 Gm. daily. During the period of this administration the capillary fragility showed an increase from 15 to 24 petechiae (in a fifteen minute test). The albumin content of the serum was noted to decrease from 5.6 to 4.7 mg. per hundred cubic centimeters during the period of administration. The clot retraction time varied from thirteen minutes to two hours and twenty-three minutes, the final time being fifty-five minutes. The coagulation time varied from two and a half to ten minutes, the final time being five minutes. The determination of erythrocytes, hemoglobin and leukocytes showed no significant changes which could be considered due to the cevitamic acid.

Comment.—This child is apparently suffering from thrombocytopenic purpura haemorrhagica. During confinement to bed the purpuric spots cleared up, possibly owing to the lack of trauma. On the other hand, the capillary fragility test showed a slight increase rather than a decrease in the number of petechiae. The decrease in the amount of serum albumin is also worthy of note. When the patient was allowed to be up a few new purpuric spots appeared. We do not feel that the administration of cevitamic acid had a favorable effect on the course of this patient's illness.

CASE 3.—J. W., a boy aged 6½ years, was admitted to the hospital during an interval in a history of repeated episodes of the appearance of purpuric spots and bleeding from the mucous membranes since Dec 1, 1931. There was no family history of bleeding in this case, and very rarely was a platelet count found to be abnormally low.

Physical examination gave essentially negative results, except for the purpuric spots. The fragility test of the red cells repeatedly gave normal results.

At the time of the present admission the patient was free from symptoms, and only 8 petechiae were found within the circle (fifteen minutes). The patient received 0.1 Gm. of cevitamic acid intravenously. During this time, the platelet count varied from 240,000 to 20,000, the last two counts being 20,000 (eleventh day) and 80,000 (fourteenth day), showing a decrease rather than an increase during the time of administration. The capillary fragility changed very slightly, but the last reading was also 8. The serum albumin showed no appreciable change, being 5.1 mg. on the third day and 5 mg. on the twelfth day of medication. The clot retraction time showed a steady increase from seventeen minutes to one hour and thirty minutes during the treatment. The coagulation time varied from nine minutes to four minutes, the final time being nine minutes. The erythrocytes, hemoglobin and leukocytes showed no significant changes which could be attributed to the cevitamic acid therapy.

Comment.—As this patient had no symptoms or signs of his purpuric disease at the time of admission, it has been difficult to estimate the action of cevitamic acid in this case. Certainly it did not produce a favorable effect on the platelet count. There was no definite change in the number of petechiae or in the amount of the serum albumin.

We are somewhat at a loss to classify this case satisfactorily, because of the continued high platelet count with very few exceptions during the four years and because of the lack of family history. We feel that the patient must be observed over a much longer period before a definite diagnosis can be established.

TRUE HEREDITARY HEMOPHILIA

The last group to be considered is composed of patients with true hereditary hemophilia. As may be seen from chart 7, the two patients showed quite opposite results following the use of cevitamic acid intravenously. Patient M. P. showed a very unsatisfactory result from the point of view of clinical course and capillary fragility, while patient T. N. improved clinically and the capillary fragility became steadily less. Several explanations for this paradoxical picture suggest themselves. One is that these patients were following the normal course of their disease, and one was entering a phase of relapse and the other a state of remission. Another possibility is that the cevitamic acid may have exerted a favorable effect on the patient (T. N.) with true hemophilia only, whereas, in patient M. P., in whom thrombocytopenia had recently developed also, the cevitamic acid failed to exert a favorable influence, just as it failed in the purpuric group.

Case 1.—M. P., a boy aged 5½ years, was considered to have familial hemophilia. His maternal uncle was known to be a bleeder and died at the age of 18 years of an intestinal hemorrhage. When the patient was 13 months old he fell from his crib and bled severely from the nose. Since that time bruising with minimal trauma had been repeatedly noticed. The first admission to the hospital was for hemarthrosis following a blow to the left knee (May 31, 1932). Treatment was symptomatic. The second admission occurred on May 2, 1934, for tarry stools and acute tonsillitis. On this occasion, in addition to symptomatic therapy there was a transfusion of 350 cc. of whole blood. The third admission, on June 14, was for hormone therapy under Dr. Marshall Pease's supervision. Theelin was administered in large doses, with no noticeable effect. Transfusion had to be employed twice. Pentnucleotide was tried on this occasion, too, but with no result. The physical examination, up to the time of the last admission, had generally given negative results, except for local evidences of hemorrhages, at the joints, nose and lips or subcutaneously.

The history preceding the present admission was as follows: Three weeks after the last discharge from the hospital, the patient bumped his head against a door, and two large hematomas developed and slightly closed black eyes. About two weeks prior to his admission (October 11), the child contracted severe bronchitis, with a temperature of 103 F. and severe anorexia. He had lost 4 pounds

(1.8 Kg.) in weight in the previous two weeks. There was no hematuria or tarry stools. The patient had picked at a scab on his lip three hours before admission, and it was still bleeding.

On physical examination the patient appeared undernourished and underdeveloped and looked chronically ill. There were scattered ecchymoses all over the body. Examination of the head revealed the presence of a few shotty occipital glands. The mucous membranes were pale, the lips bleeding constantly, and the tonsils were enlarged. Shotty cervical glands were present. Examination of the

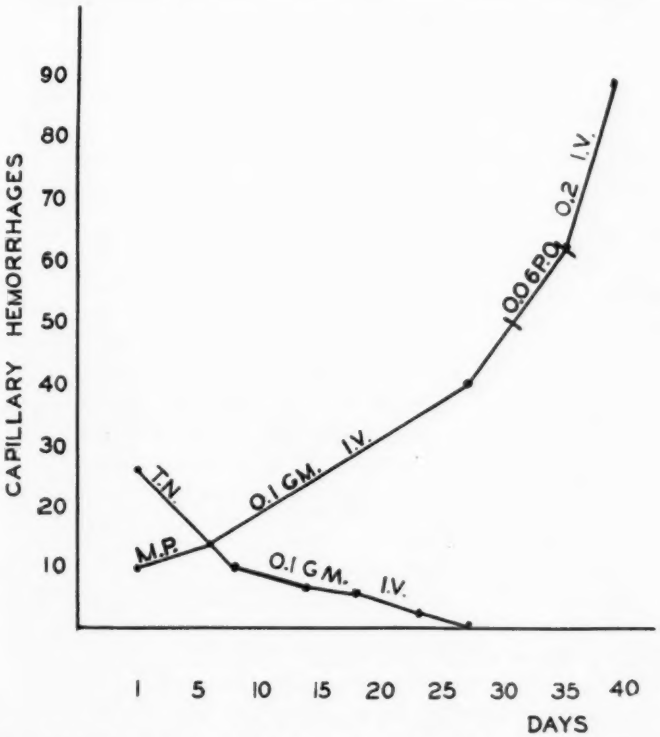

Chart 7.—The effect of cevitamic acid on the capillary fragility in two cases of hereditary hemophilia.

abdomen showed the spleen to be 2 fingerbreadths below the costal margin in the axillary line and the liver 1 fingerbreadth below the costal margin. Examination of the extremities, except for many ecchymoses, gave negative results. This patient has been followed with fairly frequent blood studies since May 1932. The number of erythrocytes has varied from 1,500,000 to 4,300,000, the final count being 2,420,000. The hemoglobin has varied from 77 to 26 per cent (Sahli), the last reading being 26 per cent. The leukocyte count has varied between 5,200 and 19,800, the last count being 8,400. The differential count has never been significant. The platelet count has been of special interest. At the time of the first admission (1932) three counts were made, the results being 210,000, 220,000 and

255,000, respectively. In July 1934 the boy was admitted to the hospital with a platelet count of 1,500, which rose as follows: in three days, to 2,200; in ten days, to 2,600; in seventeen days, to 18,300; in twenty-five days, to 22,500. Numerous platelet counts taken since then have shown a level around 60,000 to 90,000 with one brief, unexplained rise to 170,000, which soon subsided. The final count was 80,000. The bleeding time has varied from nine minutes to ten hours and forty minutes, the final time being three hours. The coagulation time has varied from seven minutes to four hours and fifty minutes, the last time being one hour and twenty minutes. The clot retraction time has varied from one hour to six hours, the last time being one hour and twenty-seven minutes. The standardized tourniquet test was not done on previous admissions, but during the administration of cevitamic acid it steadily rose from 10 petechiae to 14, to 40, to 61 and finally to 87 petechiae within the circle (chart 7). The albumin content of the serum increased from 4.4 mg. to 4.7 mg. during therapy with cevitamic acid. The globulin content showed no significant change.

Since the first admission the patient has had a series of treatments with theelin, pentnucleotide and, finally, cevitamic acid. Cevitamic acid was given as follows: 0.1 Gm. intravenously daily for thirty days; 0.06 Gm. by mouth for five days and 0.2 Gm. intravenously daily for four days. The last blood determinations noted here were made at the end of the cevitamic acid therapy. It may be said that the therapy did not appear to influence favorably the findings in the blood or the clinical course to any significant degree.

Comment.—There are several points of exceptional interest in relation to this patient. He has the family history typical of hemophilia, his hemorrhagic diathesis being transmitted through the mother but found in a male member of a former generation. At the time of his first admission he had a normal platelet count characteristic of hemophilia, but, curiously, since July 1934, the platelet count has always been markedly depressed. He has been treated by various methods, including transfusion, hormone therapy (theelin) and pentnucleotide, with no definite effect. Although it has been reported from Germany that the syndrome of hemophilia has been favorably influenced by the use of cevitamic acid, we gave this child 0.1 Gm. intravenously for thirty days, 0.06 Gm. by mouth for five days and 0.2 Gm. intravenously for four days, without demonstrable effect on the clinical course. The capillary fragility increased steadily from 10 to 87. We must therefore conclude that in this case at least cevitamic acid did not exert a favorable effect on the course of the disease. It may be noted that the albumin content of the serum, which has been reported as being elevated by the administration of cevitamic acid, was 4.2 mg. per hundred cubic centimeters on Nov. 24, 1934; 4.4 mg. on December 7, and 4.7 mg. on December 17.

Case 2.—T. N., a boy aged 6 years, represents the second instance of familial hemophilia in our series, the patient's maternal uncle, aged 33, being a known bleeder. The patient had a marked tendency to bleed from the mucous membranes and to bruise easily since the age of 1 year. The boy had been frequently readmitted to the New York Post-Graduate Medical School and Hospital during the previous two years with episodes of bleeding. At the time of this admission

he showed extensive ecchymoses of the extremities; the spleen was just palpable. He had a large tender swelling on the right side from the groin to the costal margin. He had previously been treated by transfusions and ovarian extract without demonstrable effect. He received cevitamic acid, 0.1 Gm. intravenously for one week. During this total time the capillary fragility test showed a steady reduction from 25 petechiae in fifteen minutes to 1 petechia in the same time.

The number of erythrocytes during treatment with cevitamic acid varied from 4,010,000 to 3,150,000 (last count). The hemoglobin content varied from 78 to 60 per cent (last count). The number of leukocytes varied from 4,700 to 8,850 (last count). The differential count was normal. The platelet count varied from 118,000 to 280,000 (last count). The coagulation time varied from ten minutes to five hours and fifteen minutes, the last time being twenty minutes. The clot retraction time varied from two hours and twenty minutes to twenty minutes, the last time being sixty-one minutes. None of these findings showed a definite curve of either improvement or retrogression. The serum albumin, determined on the second day of treatment, was 5.5 mg.; on the twenty-ninth day it was 4.3 mg. per hundred cubic centimeters, an actual reduction during treatment. On the twelfth day of treatment otitis media developed on the right side, for which myringotomy was done. At that time treatment with cevitamic acid was omitted for five days. At the end of the five days a transfusion of 300 cc. was given. The clinical course showed definite improvement during the patient's stay in the hospital.

Comment.—This patient showed a more favorable course during the period of therapy with cevitamic acid. The purpuric spots cleared up, and the increased capillary fragility returned to normal. There was no demonstrable effect on the platelet count. The serum albumin content actually decreased during the therapy, a fact which would tend to indicate that in this type of case it is not essential, as has been suggested by foreign workers, for the amount of serum albumin to increase in order to produce favorable effects on the bleeding. Another point of interest is the fact that a definite infection developed during the time that the child was receiving large doses of cevitamic acid, thus demonstrating that this therapeutic agent was evidently not of sufficient value in this regard to protect the patient from an active infection, although the factors of reduced general resistance and overwhelming infection must be considered. Following the clinical course of this patient through this single episode, one might be inclined to conclude that cevitamic acid exerted a favorable effect on hemophilia. We know, however, that many spontaneous remissions occur in these cases, and in view of the report of the first case in this series (hemophilia), we must entertain a very decided skepticism as to the real value of cevitamic acid in cases of this disease.

CASE 3.—J. V., a boy aged 28 months, had been seen repeatedly in various hospitals and after study a diagnosis of hemophilia was always made, although the family history revealed no other bleeders. From the age of 3 months the child had showed an abnormal tendency to hemorrhage or to bruise from the slightest trauma. He had repeated epistaxis and hematuria and purpuric spots, all of which were unaffected by therapy. He had always received a liberal amount of

citrus fruit juices. In June 1933 hemarthrosis of the left knee developed. In June and July 1933 he received ovarian extract, 4 Gm. daily, for three weeks, without effect. At that time, the tuberculin, Schick and Wassermann tests were negative. In August 1933 the right knee and thigh became markedly swollen, tender and painful on motion. They were neither red nor discolored. The child had received a series of injections of whole blood into the buttocks (the exact number is not known) with no effect and had begun to receive injections of theelin, 0.5 cc. intramuscularly, twice a week, several weeks preceding this episode. He was readmitted to the hospital on Aug. 3, 1933, with many ecchymotic spots on the abdomen, extremities and scrotum, from 2 to 5 cm. in diameter. The right knee was twice the normal size, painful, tense and held flexed. It was not discolored. A roentgenogram showed no evidence of destruction of the bones or epiphysis. From the time of admission until October 30 (twelve and one-half weeks) he received 1 cc. of theelin twice a week intramuscularly and calcium lactate, 5 grains (0.324 Gm.), three times a day orally. Throughout this time there was no consistent change in the clinical picture. There were recurrent epistaxes, ecchymoses and exacerbation of the hemarthrosis of the right knee, which was in a cast most of the time. The left knee continued to be held in a semiflexed position and was painful to move, although there were no exacerbations. The patient was discharged on October 30. He was followed in the clinic, showed no improvement and was readmitted to the hospital on Oct. 30, 1934, for therapy with cevitamic acid. He was given twelve doses of 0.1 Gm. intravenously and took 3 tablets of 0.01 Gm. by mouth for fourteen days. This series was given over a period of fifty days. Clinically, there was a very marked improvement. The ecchymoses and epistaxis ceased, and both joints cleared up entirely, so that he was able to walk and to run for the first time in his two years under observation. This improvement has been maintained until the time of writing (one month later). During his period of observation (two years) the blood picture has fluctuated somewhat but without showing apparent response to any therapeutic agent, including the cevitamic acid. The erythrocyte count has varied from 2,800,000 to 5,000,000, the last count being 4,200,000 (after cevitamic acid therapy). The hemoglobin content has varied between 46 and 83 per cent, the last value being 74 per cent. The leukocyte count has varied between 6,100 and 14,500, the last count being 9,000. The differential count has not been significant. The platelet count has varied from 173,000 to 420,000, the last count being 420,000. The coagulation time has varied from twenty-four minutes to four minutes, the last time being eleven minutes. The bleeding time has varied from four and a half minutes to immediately, the last time being half a minute.

The capillary fragility was studied during the period of therapy with cevitamic acid, and these results were obtained: controls, from 15 to 16 petechiae (seven and a half minutes); third day, 14 petechiae; sixth day, 8 petechiae; eighth day, 7 petechiae; tenth and eleventh days, 8 petechiae; fourteenth day, 17 petechiae; twenty-seventh day, 12 petechiae; thirty-seventh day, 12 petechiae; thirty-eighth day, 8 petechiae; forty-fourth day, 10 petechiae, and forty-ninth day, 8 petechiae. Because we are not convinced that familial hemophilia is the correct diagnosis, these readings are intentionally omitted from chart 7.

Comment.—This case is especially interesting because the symptoms might well fit the picture of hemophilia, but there is no family history of bleeding. There was a consistently normal or high platelet count. The patient had always used a plentiful amount of citrus fruit juice. He was under the care of the same physician for over two years and

received a variety of treatments without effect. Cevitamic acid, given intravenously and by mouth, produced a prompt remission of symptoms. It was planned to give this only intravenously, but the veins had been so mutilated by previous intravenous work that daily injections were impracticable. It is possible, however, that the intravenously administered cevitamic acid only was effective, and that we are dealing with one of the group of persons who are unable to utilize vitamin C, even though the oral intake is theoretically adequate.

An almost exact replica of this case has been studied by Dr. Barber of Alexandria, La. In a personal communication, he reported the same type of encouraging results with the use of cevitamic acid intravenously. There was, however, a relapse with a return of subcutaneous hemorrhages and hemarthrosis when the patient was given cevitamic acid orally.

Three patients with aplastic anemia with profound hemorrhages have been treated with cevitamic acid intravenously, without apparent effect. All three cases terminated fatally.

COMMENT

It was to be expected that our findings would differ in some respects from those of the foreign observers previously cited, as their reports were on very small groups of cases. We studied the serum proteins in four of our cases during treatment, and while our readings agree with those of Böger and Schroeder in that the changes in the amount of serum globulin were of no significance, three of the four cases showed a decrease in the amount of serum albumin. This is contrary to their findings of a definite increase in the serum albumin content in patients with hemorrhagic conditions and also in normal persons during cevitamic acid therapy. The first patient in our group presented a typical thrombocytopenic blood picture and showed a decrease of the serum albumin content from 5.6 to 4.7 mg.; the second had purpura of an indeterminate type and showed an inconsequential decrease from 5.1 to 5 mg.; the third had familial hemophilia and showed an increase from 4.2 to 4.7 mg., and the fourth also had familial hemophilia and showed a decrease from 5.5 to 4.3 mg. These patients were receiving a daily dose of cevitamic acid of from 0.1 to 0.2 Gm. intravenously (with rare omissions for various reasons), and they were observed not less than sixteen days, the longest period being forty days. It is therefore evident that an increase in the amount of serum albumin does not always follow therapy with cevitamic acid.

Although a large percentage of our patients were studied for all or part of the blood findings (bleeding time, clot retraction, coagulation time, platelet count and leukocyte count, including a study of the distribution), the results following cevitamic acid therapy were considered

neither uniform nor significant enough to warrant either conclusions of value or their detailed inclusion in this report. The red blood cell count and the hemoglobin content tended to show a slight, consistent rise in the cases of vitamin C deficiency but not in the other groups of cases.

It was interesting to note that while this, like all other vitamins, has been suggested as a preventive for infections of the upper respiratory tract, in one of our patients (with hemophilia) sore throat and otitis media developed, for which myringotomy was performed during the time he was receiving 0.1 Gm. of cevitamic acid intravenously each day. The factors of overwhelming infection and reduced resistance, might, however, be considered as outweighing such an influence in any individual case. We feel, therefore, that a deferred conclusion as to the value of the substance in the treatment of conditions not due to vitamin C deficiency is justified at this time.

In view of our results and the reports of others, it is felt, however, that cevitamic acid has been demonstrated to be of great value in cases of scurvy and allied conditions, dependent on vitamin C deficiency. It is true that frank scurvy is relatively rare in adults, although, as has been already pointed out, even some of these cases are not recognized. We do not feel that early or "subclinical" scurvy is a rare disease, even in a large center of civilization. The only symptom may be bleeding gums, frequently diagnosed as pyorrhea. In addition to our own experience, which has been revealed in the number of cases recognized since we became "scurvy conscious," it has been the experience of many of our associates that they, too, began to see more of these patients after their attention had been recalled to this syndrome. In this era of poverty and unbalanced faddists' diets, this group is probably on the increase. In addition, there is the large group represented by those on fruit-free diets because of ulcer, colitis or urticarial treatment, in whom "subclinical" or even frank scurvy may develop. Schultzer[47] obtained interesting results as follows: Nine of eighteen patients with ulcer with normal capillary resistance, after having been on a diet deficient in vitamin C for about sixteen days, showed lowered capillary resistance; another series of seventeen patients confirmed this result; not all showed lowered resistance because of the different length of time required to produce the syndrome in different persons; in five patients the capillary resistance was restored to normal by the addition of vitamin C (tablets of pulverized dog rose berries, not cevitamic acid); in two cases this result could not be obtained. Schultzer did not, however, express the belief that C avitaminosis is an etiologic factor in the production of gastric ulcer.[48]

47. Schultzer, P.: Hospitalstid. **77**:1052 (Sept. 25) 1934; abstr., J. A. M. A. **103**:1998 (Dec. 22) 1934.

48. Schultzer, P.: Hospitalstid. **77**:1190 (Oct. 30) 1934.

To this whole scorbutic group, cevitamic acid would seem to be of value, especially to those who, for whatever reason, cannot or will not take fruit juices. Under our guidance it has been tolerated when taken by mouth in five cases of gastric or duodenal ulcer during the acute posthemorrhagic phase (one of these is reported here). Seven patients with ulcerative colitis have taken it by mouth without any evidence of intestinal irritation. Two adult patients who were forbidden citrus fruits because of sensitivity have been able to take it without urticarial symptoms. We have administered it with excellent results to two infants who could not tolerate citrus fruit juice. We feel that all patients on a diet poor in vitamin C should be given cevitamic acid as a protective measure, unless a specific contraindication should arise.

It should be pointed out that several patients who proved to have scurvy on the basis of careful dietary history, physical signs, clinical development, capillary fragility and response to vitamin C, had previously, because the blood picture was not typical of a specific purpura, been considered to have purpura of an undetermined type. Probably many more instances of this syndrome are wrongly diagnosed.

The question of dosage cannot be completely answered on the basis of the limited total experience with this substance. In our series a patient with extremely severe scurvy was cured by the use of 0.06 Gm. of cevitamic acid daily by mouth. The patient with the next most severe condition seemed to require 0.09 Gm. daily by mouth. To a third patient we gave as high as 0.12 Gm. by mouth daily. This patient had a digestive upset on the second day, with nausea and diarrhea. Although no other cause could be found for this upset, it is questionable whether the cevitamic acid was responsible, because the same patient started to take 0.12 Gm. a few days later and was able to continue without any signs of gastro-intestinal distress.

Although a few former workers have given over 100 mg. a day or from 150 to 200 mg. every other day intravenously, we gave four of our patients 200 mg. a day intravenously, one for as long a time as fourteen days. These patients were all children and weighed 60 pounds (27.2 Kg.) or less. No injection in our entire series ever produced any evidence of a reaction. Because we are dealing with a substance which is destroyed by heat and hence cannot be completely sterilized, this phenomenon is all the more interesting. We have dissolved the contents of a vial (100 mg.) in from 5 to 10 cc. of sterile distilled water or sterile physiologic solution of sodium chloride and injected it slowly. We have not determined what the maximum tolerated dose will be or what the effects of actual overdosage would be.[49] Certainly, the range

49. We have since administered 1,000 mg. intravenously daily for periods of fourteen days and 2,000 mg. intravenously on several occasions without untoward effects.

between the therapeutic and the toxic dose is very wide. The present substance is irritating if injected into the tissues, but a newly modified preparation is reported to be suitable for such use. The present preparation may be used subcutaneously or intramuscularly if the following technic is utilized: Dissolve the cevitamic acid in sterile water and neutralize with one-half its quantity of sodium bicarbonate (yielding a solution about p_H 7). The dissolving and neutralizing should be done immediately before administration to avoid loss of effectiveness.[50]

The minimum dose of cevitamic acid required as a preventive has yet to be determined. At present, it seems that from 20 to 30 mg. should be adequate. Probably considerably less will prove sufficient. No laboratory or physical finding has been nearly as helpful in following the clinical course of this group of patients as the capillary fragility test standardized as described.

CONCLUSIONS

A crystalline substance, cevitamic acid, has been identified, isolated and synthesized. It is identical with crystalline vitamin C.

This substance has proved to be of great value in the treatment of scurvy and other evidence of vitamin C deficiency.

Its value in the treatment of thrombocytopenic purpura or familial hemophilia is doubtful.

Further studies will be necessary to evaluate its status in the treatment of many other conditions which have been reported as favorably influenced by this substance.

A standardized modification of the tourniquet test for capillary fragility, which has been found most useful in the study of these cases, is presented.

Cevitamic acid can be used safely for patients with gastric or duodenal ulcers and patients with severe ulcerative colitis.

Cevitamic acid can be used by certain patients who are unable to take citrus fruit juices because of sensitivity and by certain infants who cannot tolerate citrus fruit juices.

Cevitamic acid should be added to all diets poor in vitamin C as a preventive.

Many cases of early and "subclinical" scurvy are not recognized.

There are two groups of these patients: those whose intake of vitamin C is inadequate and those who are unable to utilize vitamin C, even though the intake is adequate.

The latter group may, for the most part, be successfully treated by cevitamic acid administered parenterally.

Dosage, tolerance and methods of administration have been discussed.

50. Fisher, B. H., and Leake, C. D.: The Parenteral Administration of Cevitamic Acid (Ascorbic Acid) Solutions, J. A. M. A. **103**:1556 (Nov. 17) 1934.

ADRENAL INSUFFICIENCY RESULTING FROM PARTIAL OR TOTAL ATROPHY OF THE ADRENAL GLANDS

EARLY CLINICAL RECOGNITION

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Disturbances in adrenal function have thus far been recognized only at relatively late stages. The reason for this apparently is twofold. First, Wilks' [1] paper, in which he rearranged and reclassified the cases on which Addison's [2] original report was based, excludes all but those cases which can be placed in a very limited category. For instance, Wilks did not accept cases without pigmentation or without tuberculosis of the adrenal glands as being instances of Addison's disease. Thus he influenced adversely the recognition and diagnosis of partial adrenal insufficiency by the elimination of all cases but those with clearcut symptoms.

A second reason is that adrenal insufficiency, although constantly present to a degree, is openly manifest only at intervals over a given period of years. Thus, patients suffering from this disease receive an array of diagnoses, some of which are erroneous but all of which detract from adequate study of the underlying disturbance. Accordingly, rather than progressively earlier recognition, the diagnosis continually is made in the late, terminal stages only.

It is thus with emphasis on the feasibility of early clinical recognition of the lesser degrees of adrenal insufficiency that the material contained herein is presented.

REVIEW OF THE LITERATURE

The fact that cases of adrenal insufficiency which satisfy the strict criteria established by Addison and Wilks represent only one of the many possible varieties is emphasized in both early and recent literature. Wilks, for instance, in 1862 stated that "Doctor Addison was impressed with the belief that the constitutional symptoms existed long before the

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1. Wilks, S.: On Disease of the Supra-Renal Capsules or Morbus Addisonii, Guy's Hosp. Rep. **8**:1, 1862.

2. Addison, Thomas: On the Constitutional and Local Effects of Disease of the Suprarenal Capsules, London, S. Highley, 1855.

discoloration of the skin." Indeed, "he was led to the fact of certain patients dying without discoloration, in whom the changes of the morbid material of the capsules had not reached that final degree which is sometimes met with."

Rowntree [3] and others indicated the possibility of the existence of early manifestations in their recognition of a "period of initial destruction of the suprarenal glands." They did not ascribe definite symptoms to this period but stated that the symptoms of asthenia, pigmentation and loss of weight and strength mark the onset of the second stage, namely, the one in which the functional activity of the adrenals is insufficient for the daily physiologic requirements. In contrast to this, it is my belief that many characteristic symptoms are presented by patients in the interval between the onset of the destructive processes in the adrenals and this "second period," which later appears to be rather the initiation of the terminal stage.

The existence of early clinical indications of adrenal insufficiency is substantiated by certain case reports. In Brenner's [4] first case, the symptoms, undoubtedly associated with adrenal insufficiency (as interpreted with respect to the behavior of our patients), were responsible for an appendectomy at the age of 28 years for "chronic appendicitis," "pneumonia" at 29 and "gastric influenza" a year later, not long before death occurred from disease of the adrenal glands. In Brenner's second case the patient had dyspepsia, with occasional vomiting, steady loss of strength and increased pigmentation following a severe mental shock one year previously. The patient became weaker and more bronzed over a period of two years, with attacks of abdominal pain later in the disease. In Wells' [5] fourth case, the patient, 51 years old at the time of her death, had been under observation for more than four years. The onset of the symptoms followed a strict regimen attendant on an attempt to lose weight. Brown spots on the legs and asthenia soon occurred and, together with low blood pressure, continued practically unchanged in spite of treatment until her death. Pain between the shoulder blades was a prominent feature at one time.

A discordant note regarding the correctness of the diagnosis, even in the face of the classic symptoms of Addison's disease, is struck by Harrop,[6] who obtained atypical clinical response to treatment with

3. Rowntree, L. G., and Snell, A. M.: A Clinical Study of Addison's Disease, Mayo Clinic Monographs, Philadelphia, W. B. Saunders Company, 1931.

4. Brenner, O.: Addison's Disease with Atrophy of the Cortex of the Suprarenals, Quart. J. Med. **22**:121, 1928.

5. Wells, H. G.: Addison's Disease with Selective Destruction of the Suprarenal Cortex, Arch. Path. **10**:499 (Oct.) 1930.

6. Harrop, G. A.; Weinstein, A.; Soffer, L. J., and Trescher, J. H.: The Diagnosis and Treatment of Addison's Disease, J. A. M. A. **100**:1850 (June 10) 1933.

adrenal cortex extract. The excellent results of Hartman,[7] however, even in the cases apparently not of gross adrenal involvement, would make one suspect that failure to obtain results was caused by use of an impotent extract.

Experimental work with the adrenal glands of animals confirms the impression from clinical sources that minor degrees of adrenal insufficiency are recognizable from the symptomatology. Hartman, for instance, reported that lesser degrees of adrenal insufficiency, produced by the maintenance of adrenalectomized cats on insufficient doses of cortical hormone, cause such symptoms as gradual loss of weight, decrease in resistance to cold and more ready fatigability. Laboratory studies reveal correspondingly slight but definite changes. In rats with chronic adrenal insufficiency but with no marked symptoms, Wyman and Walker [8] reported that the blood sugar content was maintained at a low level of the normal average, occasionally dropping below the normal. Geiling and Britton reported a fourfold susceptibility to insulin in rats with chronic adrenal insufficiency with no increase in blood sugar following hypoglycemic convulsions produced by insulin. Swingle and others [9] reported an increase in phosphorus, protein, nonprotein nitrogen and urea and a decrease of sugar in the blood of adrenalectomized cats.

Thus, even though the majority of the early symptoms are those usually associated with clinical conditions bordering on functional diseases, it is believed that their proper evaluation provides the means for the clinical recognition of partial and total adrenal insufficiency.

REPORT OF CASES

The case reports are presented in detail not only to stress the varied early manifestations of the disease but to provide an adequate basis on which a description of its early symptomatology may be built.

CASE 1.—A. G. was first admitted to the Boston Psychopathic Hospital on Feb. 9, 1925, at the age of 20. At that time the past history revealed that he had been very ill at the age of 6 months with a questionable gastro-intestinal disturbance. A discharge from an ear, which began in early childhood, continued until he was 18. He had diphtheria at the age of 4 or 5 years. As regards his personal history, he remained alone for the most part, having only an occasional friend and never mingling with any of his brothers' or sisters' friends.

The immediate reason for his admission to the hospital was an illness characterized by fever, rapid respiration and incontinence of urine and feces. He

7. Hartman, F. A.: Studies on the Function and Clinical Use of Cortin, Ann. Int. Med. **7**:6, 1933.

8. Wyman, L. C., and Walker, B. S.: Studies on Suprarenal Insufficiency: Blood Sugar in Suprarenalectomized Rats, Am. J. Physiol. **89**:215, 1929.

9. Swingle, W. W.: Blood Changes Following Bilateral Epinephrectomy in Cats, Am. J. Physiol. **79**:666, 1927. Swingle, W. W., and Pfiffner, J. J.: Adrenal Cortical Hormone, Medicine **11**:371, 1932.

neither answered questions nor cooperated in any way with the examining physician. He was apparently conscious but confused. The opinion of the physician who saw him before admission to the hospital was that his was "an acute illness of the encephalitis type."

Physical examination on admission to the hospital revealed a flushed, stuporous, almost comatose white youth with rapid pulse and respiration. The pupils were slightly irregular but reacted fairly well to light. The eyes were turned to the left but did not oscillate. The right tympanic membrane was red and crusted. The Kernig sign was negative; the neck was not stiff. The left arm and leg were flexed, and the head was turned to the left. Deep and superficial reflexes were absent. The pubic hair was of feminine distribution. The blood pressure was 110 systolic and 70 diastolic.

The urine was normal. The white blood cell count ranged between 8,000 and 14,000 cells per cubic millimeter. The temperature reached a maximum of 102 F. daily. Examination of the cerebrospinal fluid on Feb. 10, 1925, revealed 5 lymphocytes; the test for globulin gave negative results; sugar content was 330 mg. per hundred cubic centimeters of fluid; the total protein, 18 Gm. per liter, and the colloidal gold curve negative. The Wassermann reactions of the blood and spinal fluid were negative. A blood culture taken on admission was reported negative on the ninth day. A Widal test gave negative results on February 10. A series of determinations of blood sugar gave results as follows:

	Blood Sugar, Mg. per 100 cc.	Comment
February 11	52	Fasting
12	167	After administration of dextrose for 18 hours
13	86	Fasting
14	74	Fasting
15	89	Fasting
18	103	Fasting

A determination of the mental status was made several days after the patient's admission. He lay quietly in bed, taking little interest in his environment; he initiated very little talk but was coherent and relevant; his mood was stable; he had no delusions, hallucinations or compulsions; he was partially oriented; he showed amnesia for the period from Sunday night to Wednesday afternoon; his grasp of general information was only fair; his judgment and insight were questionable.

On February 14 it was noted that the knee jerks were elicited when reenforced. There was still the question of a Babinski sign on the right side. The face seemed weaker on the right. The chest showed rough, harsh sounds throughout. The patient complained at times of abdominal pain, but physical examination of the abdomen never revealed any abnormalities. Except for clearing of the drowsiness, the patient's condition was approximately the same after ten days as on admission, the temperature curve in particular having shown no change. Despite this, the patient was sent home at that time on the insistence of the family. It was the opinion of the members of the staff who saw the patient that encephalitis had developed in defective cerebral tissue.

Admission of the patient to the Peter Bent Brigham Hospital in April 1927 was occasioned by fever and malaise of five days' duration. A review of the history revealed that he was subject to frequent headaches and had changed glasses several times in the preceding few years because of this. Objects were seen

well close at hand but only with difficulty at distance. There were frequent colds with hacking cough but very little sputum. The illness responsible for the admission began five days previously. After twenty-four hours in bed, following a chilly sensation and a feeling of malaise, the patient got up but was still feeling weak. The cough which he had had at intervals previously returned, together with the headaches, thus necessitating his return to bed. Four days before admission to the hospital he first noted dull, steady pain over the whole abdomen generally but particularly severe below the umbilicus. Throughout this portion of his illness the pulse rate remained about 85, while the temperature reached a level as high as 102.5 F.

Physical examination showed that the pupils were equal and regular and reacted to light and in accommodation. Ophthalmoscopic examination revealed normally colored disks, which were well outlined except for the superior nasal quadrant of the right disk, which was somewhat hazy. An inconstant diastolic thrill and murmur were present over the precordium. The blood pressure was 95 systolic and 50 diastolic. The lungs were essentially clear except for harsh breath sounds near the midline on either side posteriorly. There was slight tenderness to pressure all over the abdomen below the level of the umbilicus; no organs were palpable. Gross neurologic examination gave negative results. On May 1 the blood pressure was 70 systolic and 50 diastolic.

The laboratory findings were: hemoglobin, 90 per cent (Dare); erythrocytes, 4,900,000; leukocytes, 8,300; blood smear, normal. The leukocyte count subsequently remained at about 10,000. The urine was normal except for the slightest possible trace of albumin in the twenty-four hour specimen. The Wassermann reaction of the blood was negative. Agglutination tests for typhoid and paratyphoid A and B organisms were negative on April 24 and May 2; two blood cultures at corresponding times gave negative results. No tubercle bacilli were found in the sputum. An electrocardiogram showed normal curves.

The patient's temperature reached normal on the tenth day of his stay in the hospital. A roentgenogram of the chest taken on May 3 was reported as showing flattening of the right side of the diaphragm, with an indistinct costophrenic angle on the right. There was diffuse mottling of the base of the right lung, but the lungs elsewhere were apparently normal. Following the return of the patient's temperature to normal, convalescence was rapid, so that on the eighteenth day he was discharged.

The third, and last, admission to the hospital was on July 25, 1933, at which time, after approximately eighteen hours in the Peter Bent Brigham Hospital, he died. The chief complaint was weakness. In the interval since the last admission, the patient had remained in fair health but had continued unsocial. There was no evidence of parkinsonism, but for two days prior to his admission there was spasticity of the arms, particularly of the right, together with numbness of the middle, fourth and little fingers of the right hand. There were never any cardiovascular symptoms. The patient had taken iron and liver on occasion for anemia. The present illness began five weeks prior to the patient's admission to the hospital, with the onset of a feeling of warmth and fever. There was some cough with the production of a small amount of whitish sputum. After a short period of rest in bed at home the temperature dropped from 102 F. to normal, coincident with the clearing up of "moisture," which the patient's physician found in his chest. Several attempts to get out of bed were followed in each instance by a recurrence of the fever and prostration. For several days preceding the admission, the patient had been able to take only liquid foods and had felt weak and cold.

Physical examination on the patient's arrival at the hospital this time revealed a drowsy-appearing white youth. His features were sunken; the skin, smooth and cool. The left arm was markedly spastic, and the forearm was kept flexed at a right angle. The right arm exhibited typical catatonicity. Ophthalmoscopic examination gave negative results. A presystolic rumble was heard at the apex of the heart. Blood pressure was 110 systolic and 70 diastolic. There were occasional crackles audible at the base of each lung. The blood pressure continued to fall with the passing of time, so that nine hours after admission it reached 70 systolic and 40 diastolic, and from several hours later until death it was unrecordable.

Laboratory studies revealed a hemoglobin content of 110 per cent (Sahli), 5,000,000 erythrocytes and 15,000 leukocytes, with an essentially normal differential count except for a preponderance of young polymorphonuclear cells. The urine contained a minimal amount of albumin, occasional leukocytes, 25 red blood cells per high power field and an occasional cast. The Wassermann and Hinton reactions of the blood serum were negative. The blood sugar content six hours after admission was 101 mg. per hundred cubic centimeters. Lumbar puncture revealed a low initial pressure of 30 mm. of water, a normal response to compression of the jugular vein, 2 cells per cubic millimeter of spinal fluid, negative Wassermann and colloidal gold reactions and a total protein content of 35 Gm. per liter.

At autopsy the adrenal glands could not be palpated, the pancreas was approximately normal and the thymus was small. The heart, which weighed 210 Gm., appeared normal except for the mitral valve; this showed slight stenosis, the circumference of the valve measuring 4.2 cm. The lungs on the cut surface showed yellowish nodules from 2 to 3 mm. in diameter, scattered throughout the lung tissue but with the majority at the base. The liver, weighing 1,180 Gm., appeared to contain more fat than usual. Two portions of tissue from the region of each adrenal gland were described as possessing very little cortical tissue and a soft, pale, more yellowish type of medullary tissue than usual. No additional adrenal tissue was identified in the usual position. The testes were smaller and softer than normal, each weighing 19 Gm. The thyroid gland was extremely atrophic, weighing only 4.5 Gm. but presenting the usual lobes and an isthmus. The two parathyroid glands appeared normal. Examination of both the brain and the spinal cord before and after fixing in solution of formaldehyde revealed no abnormalities.

Microscopic examination of the adrenal glands (fig. 1) showed atypical structures. There was no differentiation into cortex or medulla; instead, embedded in fatty areolar tissue were small collections of cells, the majority of which were vacuolated. Some of the vacuolated cells had increased from two to three times their normal size and contained only a narrow rim of cytoplasm around what was formerly a large vacuole. In other areas, the majority of the cells were fairly well preserved. They were polygonal and contained moderately deeply staining nuclei. The latter were embedded in homogeneous reddish-brown cytoplasm. There were all gradations from cells with small vacuoles to those composed almost entirely of a vacuole, in which case the nucleus, in signet-ring fashion, was pushed against the wall of the cell. The anterior lobe of the pituitary gland contained approximately 3 per cent acidophilic cells; the number of basophils appeared to be increased. The cells extending along the infundibulum were fairly large, swollen and vacuolated. The pineal gland was normal. The thyroid vesicles varied in size. In several areas practically all of them were small and packed with colloid. Elsewhere throughout the gland both small and large ones were in evidence. The colloid in general was normally stained. The epithelium of the acini was

cuboidal and in a few of them presented infoldings. There were numerous collections of lymphocytes throughout the gland, chiefly in the loose connective tissue. In the testes the number of interstitial cells was reduced. Those present showed neither granules nor crystalloids. Differentiation of the remaining elements of the testis had not reached the spermatid stage. The pancreas, spleen, liver and kidneys were normal. The myocardium showed an increase in brown

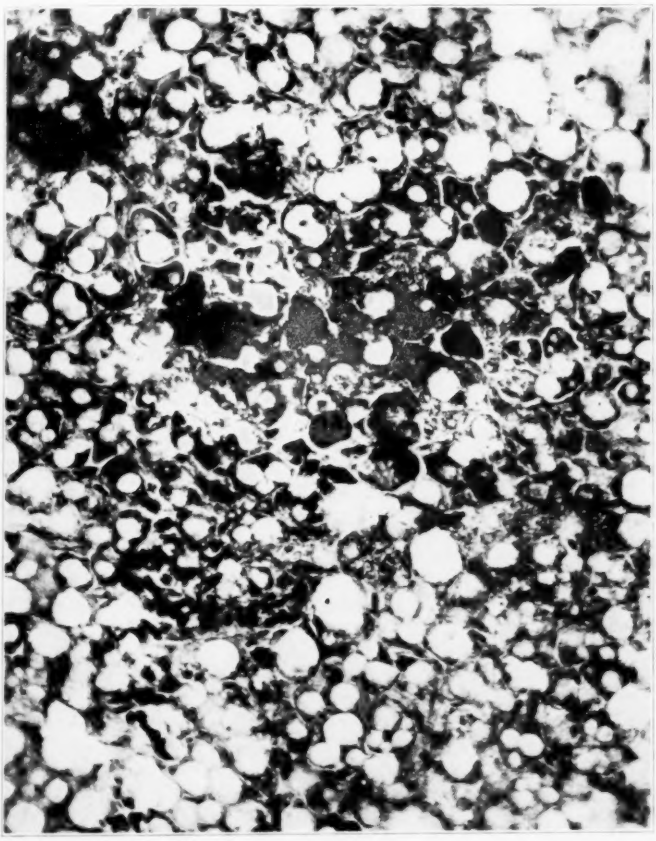

Fig. 1 (case 1).—Photomicrograph (× 300) showing the better preserved adrenal tissue. All semblance of adrenal architecture has disappeared. Only a few cells remain, the majority of which contain large vacuoles. A rare area, such as this one, contains a group of such cells.

pigment. In some areas of the sections of lung the tissue appeared normal. In others there was obliteration of the normal architecture by loose connective tissue, in which the majority of the cells which contained large fat vacuoles were interspersed with globules of fat lying free in the connective tissue. Many of the

alveoli in the more normal-appearing portions of lung were filled with similar globules. The parathyroid glands, several lymph nodes, the aorta and sections of tissue from the central nervous system were normal. A section of bone marrow showed a diminished number of cells, with the majority of the cells of the myeloid series immature.

CASE 2.—M. B. W., a girl 14 years old, was admitted to the Peter Bent Brigham Hospital for the first time in March 1916, complaining of pain in the stomach. The patient had always been in rather poor health. She had measles and chickenpox in childhood, and six months before admission, "pleurisy" in the lower part of the chest on the right side. She became dyspneic on exertion, had a hacking cough with greenish sputum since the preceding summer, was fastidious as regards her diet and ate only certain foods which agreed with her. The morning before admission to the hospital, while on her way to school, the patient was seized with a severe, sharp pain in the right upper quadrant of the abdomen, which was worse on deep inspiration. After ten hours the pain radiated "all over her stomach." The patient had been nauseated since the onset of the attack, and although most of the pain was in the right upper quadrant, appendectomy was performed twenty-four hours after admission. The results of the physical examination were essentially negative. The temperature was 102 F., the blood pressure 102 systolic and 58 diastolic and the leukocyte count 6,000. The appendix was diagnosed as normal after histologic examination.

The second admission to the hospital, the first for medical attention, occurred when the patient was 24 years old. The chief complaint at that time was vomiting. The patient at that time had been married seven years and had borne five children, all of whom were living. The systemic history revealed profuse leukorrhea since the last delivery and normal catamenia since the age of 14. She had been constantly nervous, had fainted when excited, had felt jumpy and had had twitching sensations in the hands and feet since the third delivery. She had lost 20 pounds (9.1 Kg.) during the preceding year. The onset of the present illness followed severe hemorrhages incident to retained placental tissue from her delivery six weeks previously. Uneventful convalescence, after two transfusions, was in turn followed by weakness, fatigue, vertigo and nausea at the sight of food. On physical examination the blood pressure was found to be 100 systolic and 70 diastolic. There was an involuntary twitching motion of the arms and legs, accentuated by calling the patient's attention to it. There was a coarse tremor of the extended fingers. Subsequent determinations of blood pressure one and two weeks after admission were 90 systolic and 70 diastolic and 100 systolic and 70 diastolic, respectively. There was marked subjective improvement following administration of liver and reduced iron. Changes noted in the blood meanwhile were an increase in the hemoglobin content from 60 to 70 per cent (Dare) and in the erythrocyte count from 3,700,000 to 4,400,000. The leukocyte count remained around 7,000, with 40 per cent lymphocytes.

The third admission, which occurred approximately eight months later, was occasioned by vomiting and occipital headaches. The patient meanwhile had been followed in the dispensary, where a loss of 5 pounds (2.3 Kg.) was recorded. The patient then weighed 96 pounds (43.5 Kg.). She had had no menstrual periods since discharge from the hospital. Each month, however, at about time for the menstrual period, the patient would have a spell of vomiting of from one to three days' duration. Until October 1928, the attacks of vomiting were accompanied by chills and fever, but subsequently these disappeared until the patient was admitted to the ward on their recurrence. Examination revealed a poorly developed and malnourished white woman who appeared ill. The pupils

were large and reacted to light and in accommodation. There were photophobia, pallor and blurring of the margins of the disks, with absence of cupping. On admission the blood pressure was 86 systolic and 56 diastolic. There was tenderness on palpation of the abdomen over the aorta, just to the left of the midline. The knee jerks were hyperactive. Two days after admission a strong odor of acetone was noted on her breath. Three days later the blood pressure was 92 systolic and 64 diastolic, the patient meanwhile having become increasingly drowsy, in fact, almost comatose. After a period of fasting the blood sugar content was approximately 44 mg. per hundred cubic centimeters of blood. The patient responded well to an injection of 500 cc. of a 10 per cent solution of dextrose given by hypodermoclysis and to another injection of a corresponding amount of a 20 per cent solution given intravenously. Two days later (January 10) the blood sugar content after a period of fasting was 50 mg. Subsequent determinations on January 20 and 27 showed 64 and 130 mg., respectively. The blood pressure remained low, namely from 80 to 100 systolic and from 50 to 60 diastolic. The abdominal pain recurred during the week ending February 5. The basal metabolic rate on January 28 and 31 was —24 and —32, respectively. At the end of two months the patient gradually improved so as to be able to walk unassisted, and she soon left the hospital.

The fourth, and last, admission to the hospital was of short duration. Five and one-half months after her last admission the patient returned because of vomiting. Having been fairly well previously, she began to feel fatigued six days before admission. A fever the next day was followed by nausea, vomiting and frequent severe chills; she "couldn't get warm." The blood pressure on admission was 78 systolic and 46 diastolic. The patient appeared ill and had an area of tenderness to deep pressure over the umbilicus; the abdominal reflexes were absent. The patient's course was gradually downhill; the temperature rose to 106 F., and the blood pressure became unobtainable. The blood sugar content three days before death was 87 mg.; the carbon dioxide combining power of the blood plasma was 36.3 per cent. A culture of the blood taken the day before death was negative. Examination of the urine showed a very slight trace of albumin and the slightest possible trace of acetone. The hemoglobin content and the red blood cell count remained approximately at previous levels, namely 60 per cent and 3,700,000.

At autopsy it was noted that hair was practically absent over the axillae and pubes. The breasts, somewhat pigmented, were otherwise not abnormal. There was no evidence of the presence of a thymus gland. The heart was small and the myocardium slightly more brown than usual. The spleen weighed 240 Gm. and the pancreas 51 Gm. There was a brownish tinge to the liver. The pelvic organs were normal, as was the brain. A blood culture taken at the time of autopsy was reported negative. The adrenal glands were markedly decreased to about one fifth of the normal size. Both the cortex and the medulla were narrowed, the former to a greater degree.

On microscopic examination, the architecture of the adrenal glands (fig. 2) was markedly changed, chiefly in the cortex. The glomerular zone was absent; in its place were many small flattened cells with dark pyknotic nuclei. The arrangement in groups persisted to a degree, but at the periphery nothing more than layers of elongated, dark-staining nuclei were present, and these merged with the surrounding fibrous tissue. The remaining portion of the cortical tissue, which constituted half the bulk of the adrenals, was composed of strands of small, closely packed, more or less polygonal cells. A few areas in this zone contained small adenoma-like structures in which the cells approached a more

normal appearance; that is, they were similar to the cells of the normal zona fasciculata. The polygonal outline of these cells was more readily identifiable; their cytoplasm had the more usual vacuolated appearance, and their nuclei appeared more normal than the remainder of the surrounding cells. The cells of the medulla markedly decreased in number, appeared normal except for autolysis. The adrenal gland showed practically identical changes except that those in the region of the

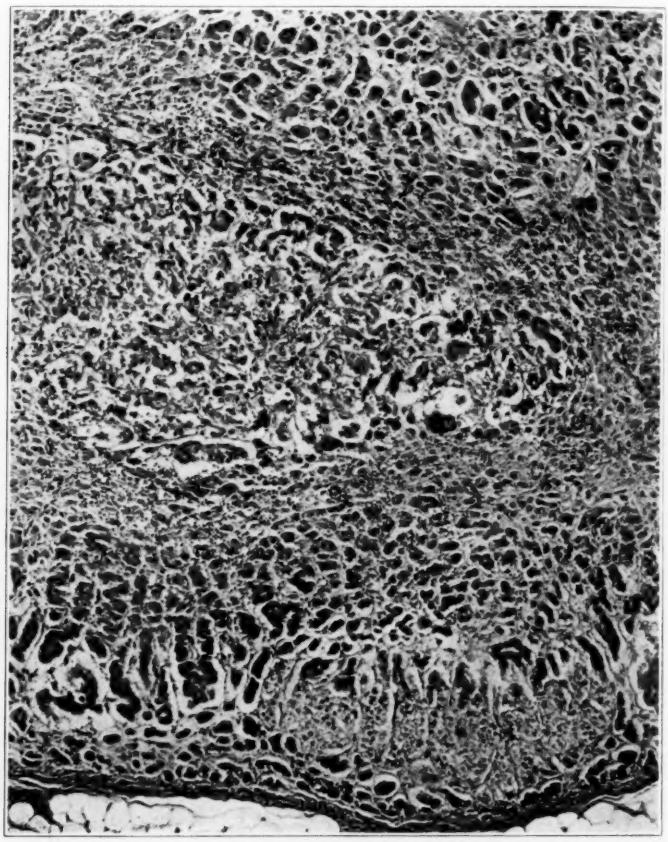

Fig. 2 (case 2).—Photomicrograph (×90) showing that semblances of the normal adrenal architecture are present, while the amount of tissue is markedly decreased. Several small regenerated areas are present.

zona glomerulosa were less marked. The thyroid gland showed areas of varied appearance. In some, the follicles approached normal size and content but were lined with cuboidal epithelium which was lower than normal. In other areas the follicles, practically free from colloid, contained more normal-appearing cells, while those of the walls presented frequent infoldings. In some regions the

connective tissue stroma was markedly increased. There was only slight infiltration with lymphocytes. In the ovary, the follicles were in all stages of development but were markedly reduced in number and embedded in an increased amount of fibrous tissue. There was central necrosis of the liver. The myocardium contained an increased amount of brownish pigment. There were a few patches in the sections of lung indicating very clearly pneumonia; the spleen was normal.

COMMENT

The cases here reported exhibit practically every feature recognized thus far, either clinically or experimentally, as an accompaniment of adrenal insufficiency.

Surpassing those cases of adrenal disease due to tuberculosis, in which the average duration is from six months to two years, in our cases symptoms were present over periods of eight and three years, respectively. In general, such cases of long duration are characterized by intervals of relatively great freedom from symptoms. One patient in Wells' series, for instance, presented exacerbations and remissions at intervals over a period of four years. Data as to the duration are, however, very probably inaccurate, because if the patient does not happen to be under the care of the physician who saw him in the first stages of the disease, there is great probability that the several disturbances will be interpreted as of different origin.

Addison's term, general languor and debility, best describes the chief symptoms present in our cases. This part of the disability was disturbing and interfered with the well-being of our patients to a marked degree, while in addition it probably accounted for their decreased motor and cerebral activity.

Gastro-intestinal upsets, as evidenced by nausea and vomiting, likewise play a significant rôle. For instance, each of the last three admissions to the hospital of our second patient was occasioned by vomiting. Further, during the period between the second and the third admission, the vomiting of the patient occurred at monthly intervals and was associated with expected but never occurring menstruation. This probably resulted from the increase in adrenal insufficiency incident to the added stress of the catamenia, which resulted in a low blood sugar content and vomiting.

Pigmentation in our patients was present only to the extent of a slight yellowish tint to the skin. There was no history or indication of bronzing of the skin. That this is, however, entirely compatible with the presence of adrenal disease is evident from one of the cases described by Wells and a case mentioned by Kaufmann.[10] In fact, certain German physicians consider bronzing of the skin a symptom of only minor importance, while, on the other hand, others hold it to be the most important symptom of the disease. In his experimental

10. Kaufmann, E.: Pathology, translated by S. P. Reimann, Philadelphia, P. Blakiston's Son & Co., 1929.

animals, Hartman noted a discoloration of body fat but said little about the occurrence of pigmentation.

Fever was present during the exacerbations of the insufficiency. During the acute phases each of the patients manifested an increase in body temperature, in one instance to as high as 107 F. The body temperature during the quiescent interval, on the other hand, remained subnormal.

Pain in the abdomen is one of the most interesting symptoms of both the cases described here and those reported in the literature. When it occurs at the time of the most marked insufficiency, usually it is located in the upper part of the abdomen on either side and is associated with tenderness on deep pressure. Even when it occurs at an early stage in the development of the disease (as in the second case), the pain possesses the same characteristics. Neither Brenner nor Wells discussed this symptom, which, however, is noted in their protocols as having occurred. Rowntree and Snell stated that abdominal pain occurs in about half of the cases of Addison's disease. In Saphir and Binswanger's [11] patient with adrenal insufficiency the pain began on the right side of the abdomen and after twenty-four hours radiated all over the abdomen. Because of this, appendectomy was performed, and while neither the appendix nor the adrenal glands showed evidence of acute inflammation, it is possible that the pain could have had a source other than an inflammatory process.

Symptoms in the central nervous system are very variable in their occurrence. When attacks of syncope, convulsions and shocklike crises occur, they are believed by Rowntree and Snell, for instance, to be on the basis of cerebral anemia incident to a marked decrease in the volume of blood. However, in our first case, just as in Rabinovitch and Barden's,[12] the spastic contraction of the right arm, which relaxed as the patient went into coma, is believed to have resulted from the hypoglycemia. Corresponding to this is the satisfactory immediate response to dextrose. Tedstrom,[13] following an analysis of a series of cases in which hypoglycemia resulted from hyperinsulinism, found that a large number of neurologic symptoms, such as occurred in our cases, are frequent in appearance.

On physical examination the patients, in general, are rather well developed and well nourished, in contrast to the obvious abnormal condition which one would expect to accompany congenital aplasia of either

11. Saphir, O., and Binswanger, H. F.: Suprarenal Cortical Insufficiency and Cytotoxic Contraction of the Suprarenals, J. A. M. A. **95**:1007 (Oct. 4) 1930.

12. Rabinovitch, J., and Barden, F. W.: Hypoglycemia Associated with a Tumor of the Islands of Langerhans and with Adrenal Insufficiency, Respectively, Am. J. M. Sc. **184**:494, 1932.

13. Tedstrom, M. K.: Hypoglycemia and Hyperinsulinism, Ann. Int. Med. **7**:1013, 1934.

the adrenal or other glands of internal secretion. Pigmentation usually is absent, but there may be a yellowish tint to the skin, with some deepening in shade of the normally pigmented areas. Hypotension is constant. At the periods when the adrenal insufficiency is most marked, the blood pressure falls to very low levels. The pupils may be large or of normal size, but usually they react normally. The optic disk may present inconstant findings suggestive of early choking, or there may be areas of pallor. The thyroid gland usually is normal but may be small. If râles occur, they are of incidental significance only. Abdominal tenderness, more or less widespread over the epigastrium, may be elicited at the time of the abdominal pain. The urinary tract is essentially normal on examination. The testicles may be small.

Pathogenesis of the Symptoms.—Certain facts obtained by experimental work, while variously interpreted in regard to the normal physiology of the adrenal cortex, serve to explain the mode of production of the symptoms which occurred in our cases. Experimentally, it is found that whether the blood sugar is below or at the usual level, there is practically no response on its part to stimuli which ordinarily evoke hyperglycemia, nor is there storage of glycogen after administration of dextrose in adrenalectomized cats. The shift in water balance (which is simultaneous with the carbohydrate disturbance), such that the liver and muscles show an increase and the blood a decrease in hydration, is readily restored to normal by treatment and is subsequently easily maintanied at that level. The fact that the latter response is so prompt, effective and continuous, whereas there is no change in the carbohydrate, even with continuous administration of saline solution, makes the disturbance of the carbohydrate phase the significant one. Clinically this interpretation holds as regards our cases, in that in both of them the onset and relief of the hypoglycemia determined the degree of the patient's prostration or relative well-being. However, there are undoubtedly additional disturbances, evident particularly by the pigmentation and the nonrelief by administration of carbohydrates in the terminal stages, of a more delicate nature, the mode of action of which is as yet undecided.

Differential Diagnosis.—All the less obvious clinical entities, both common and rare, probably have been confused from time to time with the various epochs in and the manifestations of adrenal insufficiency.

In the presence of a fair degree of development and nourishment, the patients early in the course of the disease are most likely to be eliminated from deserved study by the diagnosis of the condition as psychoneurosis. True, it is only during a period of exacerbation that a definite diagnosis can be made, but this can be accomplished, with its resultant great satisfaction, if the patient receives a thorough initial examination and adequate subsequent ones. Classifications related to neurasthenia likewise decrease the possibility of early diagnosis.

Acute appendicitis, suggested by the abdominal pain, is differentiated by a higher leukocyte count, which increases rather rapidly, localization of the pain, which might at first have been in the upper part of the abdomen, to the region of McBurney's point and the absence of neurologic symptoms. Chronic appendicitis as a diagnosis is not acceptable; in the sense of recurring acute attacks, the criteria for differentiation are identical with those mentioned under a discussion of the individual attacks.

Certain other diagnostic terms, which in themselves are open to controversy as indicating conditions in which neither the etiologic agent nor the underlying pathologic process is known, have been used to catalog the disorder from which the patient suffered early in the development of the disease. In this category are included gastric influenza and cyclic vomiting. Fortunately, such diagnoses, even though incorrect, do represent a step toward the recognition of organic disease, while at the same time they save the patient from operative procedures.

Epidemic encephalitis, probably because of its protean manifestations, is the diagnosis not infrequently made during the early stages of the disease. The manifestations which are responsible for this probably are traceable in their entirety to the hypoglycemia which is present. In the face of symptoms of the central nervous system, which include not only those noted by Tedstrom but such bizarre ones as hemiplegia, which disappears promptly with the administration of dextrose (Wechsler [14]), there is a strong possibility that adrenal insufficiency is the basis for the disturbance.

SUMMARY

The clinical aspects, including both symptomatology and diagnosis of early adrenal insufficiency resulting from partial or total atrophy of the adrenal glands, are discussed in this paper. The features stressed are: the existence of a definite but hitherto considered vague group of symptoms, from the time of onset to the termination of the destructive process in the adrenals; the manifestation of exacerbations in the adrenal insufficiency by nausea, vomiting, hypotension, hypoglycemia, drowsiness even to coma and atypical neurologic signs; the occurrence of exacerbations during periods of physical, emotional or endocrine stress; the frequent absence of pigmentation, and the relief of symptoms during the periods of exacerbation, in all but the terminal stages, by the administration of dextrose.

Dr. Henry A. Christian granted me permission to use material from the clinical records and Dr. S. B. Wolbach the autopsy material from the cases reported.

14. Wechsler, I. S., discussion on Rynearson, E. H., and Moersch, F. P.: Neurologic Manifestations of Hyperinsulinism and Other Hypoglycemic States, J. A. M. A. **103**:1198 (Oct. 20) 1934.

RELATION OF DISEASE OF THE LIVER TO ANEMIA

TYPE OF ANEMIA, RESPONSE TO TREATMENT, AND RELATION OF TYPE OF ANEMIA TO HISTOPATHOLOGIC CHANGES IN LIVER, SPLEEN AND BONE MARROW

M. M. WINTROBE, M.D., PH.D.
BALTIMORE

Attention has been directed recently in Germany,[1] Italy[2] and Austria,[3] as well as in this country,[4] to the occurrence of macrocytic anemia in association with disorders of the liver. The recognition of a hematologic picture in cases of disease of the liver resembling in many respects that of pernicious anemia is not new, as a review of the literature in an earlier communication[4a] indicated. Nevertheless, little significance was attributed to the association, and it has been only with the recently renewed interest in hematology that several investigators, working independently, have rediscovered this type of anemia.

In several respects the various observations are essentially in agreement. The anemia associated with disorders of the liver is rarely severe.[5] The macrocytosis affects the great majority of the red corpuscles,[6] which show relatively little variation in shape or size.[7] The lack of variation in the size of the corpuscles, however, does not distinguish

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1. Schulten, H., and Malamos, B.: Ueber Veränderungen der roten Blutkörperchen bei Lebererkrankungen, Klin. Wchnschr. **11**:1338 (Aug. 6) 1932.

2. Gamna, Carlo: Ueber Veränderungen der roten Blutkörperchen bei Lebererkrankungen, Klin. Wchnschr. **12**:348 (March 4) 1933.

3. Fellinger, K., and Klima, R.: Untersuchungen über Anämien bei Leberzirrhosen, Wien. klin. Wchnschr. **46**:1191 (Oct. 6) 1933.

4. (*a*) Wintrobe, M. M., and Shumacker, H. B.: The Occurrence of Macrocytic Anemia in Association with Disorder of the Liver, Bull. Johns Hopkins Hosp. **52**:387 (June) 1933. (*b*) Cheney, G.: The Morphology of the Erythrocytes in Cirrhosis and Other Disorders of the Liver, California & West. Med. **39**:90 (Aug.) 1933. (*c*) Van Duyn, John, Jr.: Macrocytic Anemia in Disease of the Liver, Arch. Int. Med. **52**:839 (Dec.) 1933. (*d*) Goldhamer, S. M.: Liver Extract Therapy in Cirrhosis of the Liver, ibid. **53**:54 (Jan.) 1934.

5. Schulten and Malamos.[1] Gamna.[2] Fellinger and Klima.[3] Wintrobe and Shumacker.[4a] Cheney.[4b]

6. Schulten and Malamos.[1] Gamna.[2] Wintrobe and Shumacker.[4a] Cheney.[4b]

7. Fellinger and Klima.[3] Wintrobe and Shumacker.[4a] Cheney.[4b]

the condition from pernicious anemia, for the distribution curves of the diameters of the red corpuscles are like those in cases of pernicious anemia with similar grades of anemia.[4a] Nucleated red corpuscles are uncommon,[4b] and the fragility of the erythrocytes is normal.[3] Spontaneous remissions and relapses of the anemia may occur.[8] On clinical as well as postmortem evidence it was stated, or at least implied, by all the authors cited that the cases which they reported do not represent the accidental association of pernicious anemia with disease of the liver. It has also been pointed out that there is no relationship between the concentration of the bilirubin in the serum and the size of the red corpuscles.[9]

There is, however, a wide divergence of opinion as to the frequency of this type of anemia, and its cause is a subject of speculation. Schulten and Malamos [1] referred to the occurrence of macrocytosis in all cases of catarrhal icterus and cirrhosis of the liver, whereas Fellinger and Klima [3] found macrocytic anemia in eighteen of forty-eight cases (37 per cent) of cirrhosis, and Van Duyn [4c] found it in only five of twenty-eight cases (18 per cent) of the latter disease. No adequate study of the nature and severity of the anemia in relation to the changes observed microscopically in the liver and in the hematopoietic organs has been reported.

In the following pages is an account of the study of one hundred and thirty-two patients who suffered from various types of hepatic disorder. In all of the cases the mean volume and hemoglobin content of the red corpuscles were measured,[10] and in the majority smears of blood were studied and other morphologic examinations were made. The observations usually were repeated at intervals. In some cases the effect on the blood of various types of treatment was studied. Gastric analysis and the van den Bergh test were carried out in a great number of cases; determinations of the icterus index and examinations of the urine for urobilinogen, urobilin and bile were made in every case. Through the courtesy of Dr. L. J. Soffer, I am able to refer to the results of tests of hepatic function (bilirubin, bromsulphalein, galactose and levulose) which were carried out by him in fifty-one of the cases. Autopsy was performed in thirty-four cases.

TYPE OF ANEMIA

The observations on anemia are summarized in tables 1, 2 and 3. The cases of hepatic disease were divided into three large groups—those of cirrhosis, malignant disease, and miscellaneous disorders—and

8. Fellinger and Klima.[3] Wintrobe and Shumacker.[4a]

9. Schulten and Malamos.[1] Wintrobe and Shumacker.[4a] Cheney.[4b]

10. Wintrobe, M. M.: Macroscopic Examination of the Blood, Am. J. M. Sc. **185**:58 (Jan.) 1933.

each of the groups was further subdivided. In addition to the thirty-four instances in which autopsy was performed, there were thirteen cases in which the diagnosis was corroborated or corrected by exploratory laparotomy. The diagnosis in each of the remaining cases was based on the observations of several physicians.

The anemia in each case was classified on the basis of the mean volume and hemoglobin content of the red corpuscles, according to criteria outlined elsewhere.[11]

In thirty cases (22.7 per cent) there was no anemia. Macrocytic anemia was present in forty-three cases, or 32.6 per cent; normocytic anemia, in forty, or 30.3 per cent; simple microcytic anemia, in three, or 2.3 per cent, and hypochromic microcytic anemia, in sixteen, or 12.1 per cent.

TABLE 1.—*Type of Anemia in Cases of Cirrhosis of the Liver*

Type of Cirrhosis	Number of Cases	No Anemia	Anemia			
			Macrocytic	Normocytic	Simple Microcytic	Hypochromic Microcytic
Nodular (Laënnec)	23	0	6 + 2 (?)*	11	0	4
Biliary	5	1	3	1	0	0
Toxic	2	0	2	0	0	0
Pigment	2	1	1	0	0	0
Syphilitic	6	3	1 (?)	2	0	0
Unclassified	6	2	3	1	0	0
Total	44	7 (15.9%)	18 (3?) (40.9%)	15 (34.1%)	0	4 (9.1%)

* In tables 1, 2 and 3, the cases of anemia which cannot with perfect certainty be classed as macrocytic, either because opportunity did not permit more than one examination of the blood to be made or because the mean corpuscular volume was only slightly greater than normal (95 or 96 cubic microns), are indicated by question marks.

The last-named type of anemia could be attributed in most instances to chronic loss of blood. Thus, among the cases of cirrhosis (table 1), hypochromic microcytic anemia was noted only in association with the nodular (Laënnec) type, in which obstruction of the portal blood vessels was associated with hemorrhage. Among the cases of malignant disease of the liver, hypochromic microcytic anemia was associated in three instances with carcinoma of the stomach, and in these cases blood was found in the stools. In a case of carcinoma of the gallbladder, ulcerations were found in the stomach and duodenum. Blood was found in the stools of one of the patients with carcinoma of the pancreas. In two of the cases recorded in table 3 in which hypochromic microcytic anemia was noted, there was a history of uterine bleeding

11. Wintrobe, M. M.: Anemia: Classification and Treatment on the Basis of Differences in the Average Volume and Hemoglobin Content of the Red Corpuscles, Arch. Int. Med. **54**:256 (Aug.) 1934.

over a long period. Thus, in all but five patients this type of anemia could be definitely attributed to the loss of blood.

In the three cases of simple microcytic anemia, the anemia was only moderate in degree, the red blood cell count averaging 3,850,000. The mean corpuscular volume was 78 cubic microns, and the mean corpuscular hemoglobin concentration, 33 per cent. One of the patients had congenital hemolytic jaundice, while in the other two there were complicating inflammatory processes.

In the cases studied, then, when anemia was noted, unless chronic loss of blood had occurred, the anemia was usually either of the normocytic or of the macrocytic type. The mean erythrocyte count in the cases in which normocytic anemia was present was 3,920,000,

TABLE 2.—*Type of Anemia in Cases of Malignant Disease of the Liver*

Diagnosis	Number of Cases	No Anemia	Anemia			
			Macrocytic	Normocytic	Simple Microcytic	Hypochromic Microcytic
Primary corcinoma	4	2	2	0	0	0
Malignant disease secondary to carcinoma of stomach	10	1	2 (?)	5	0	3
Malignant disease secondary to carcinoma of gallbladder	3	0	1 (?)	1	0	1
Malignant disease secondary to carcinoma of pancreas	14	1	2	7	0	3
Malignant disease secondary to carcinoma of miscellaneous origin	5	0	1	3	1	0
Total	36	4 (11.1%)	8 (3?) (22.2%)	16 (44.4%)	1 (2.8%)	7 (19.4%)
Malignant disease of liver associated with cirrhosis (included above)	8	1 (12.5%)	5 (62.5%)	1 (12.5%)	0	1 (12.5%)

and the mean corpuscular volume was 87 cubic microns. The mean red cell count in the group of cases of macrocytic anemia was 3,480,000, and the mean corpuscular volume, 103 cubic microns.

According to the data recorded in the tables, macrocytic anemia was somewhat more common than the normocytic type. Among the cases of macrocytic anemia were included, however, five instances of hemolytic anemia of obscure origin in which there were hepatomegaly and jaundice. In these five cases the morphologic findings in the blood were, without doubt, profoundly influenced by the destruction of the blood, and the anemia cannot be considered as fundamentally due to disease of the liver. The cases, therefore, may be excluded from the series. Among the thirty-eight instances of macrocytic anemia which remain, there are thirteen which cannot with certainty be grouped with those due to disease of the liver, either because opportunity did not permit more than one examination of the blood to be made or because

the mean corpuscular volume was only slightly greater (95 or 96 cubic microns) than normal.[11] There remain twenty-five cases (21.9 per cent) in which, without any doubt, macrocytic anemia was associated with disease of the liver. The mean red cell count in the twenty-five cases was 3,470,000 and the mean corpuscular volume, 104 cubic microns.

DESCRIPTION OF ANEMIA AND RESPONSE TO TREATMENT

The macrocytic anemia observed in association with disorder of the liver has already been described.[4a] As in pernicious anemia, the macrocytosis is, on the whole, inversely proportional to the degree of anemia. The coefficient of correlation for 163 determinations in thirty-one cases of hepatic disease with macrocytic anemia is -0.5620 ± 0.0361.

TABLE 3.—*Type of Anemia in Cases of Miscellaneous Disorders of the Liver*

Diagnosis	Number of Cases	No Anemia	Anemia			
			Macrocytic	Normocytic	Simple Microcytic	Hypochromic Microcytic
Catarrhal jaundice	8	3	1 + 2 (?)	2	0	0
Jaundice due to arsphenamine	11	2	3 + 2 (?)	3	0	1
Acute yellow atrophy	6	5	0	1	0	0
Obstruction of bile duct	3	0	2 (?)	1	0	0
Amyloid disease	4	0	1 + 1 (?)	0	0	2
Chronic passive congestion	7	5	0	1	0	1
Miscellaneous hemolytic anemia with hepatomegaly	7	1	5	0	1	0
Other conditions	6	3	0	1	1	1
Total	52	19 (36.5%)	17 (??) (32.7%)	9 (17.3%)	2 (3.9%)	5 (9.6%)

The coefficient of regression is: mean corpuscular volume equals $120.8 - 6 \times$ red cell count (in millions). These values are similar to those found in cases of pernicious anemia.[11]

Morphologic evidence of increased hematopoiesis was rarely noteworthy in any of the cases. Except in the cases of hemolytic anemia (table 3), nucleated red corpuscles were never found in the circulating blood, and even polychromatophilia was uncommon.

It has been pointed out that rapid spontaneous remissions in the blood count occur not infrequently in cases of hepatic disease with anemia.[4a] The observations reported here indicate that remissions, in which the erythrocyte count rises and the mean corpuscular volume changes toward the normal, are much more common in cases of hepatic disease with macrocytic anemia than in those with other types of anemia, such remissions having occurred in eighteen of twenty-five cases (72 per cent) of macrocytic anemia as compared with five of twenty cases (25 per cent) of the nonmacrocytic group. It should be noted that

these changes in the blood took place even though, in some instances, the rise in the erythrocyte count was contrary to the general course of the patient's illness.

Only in the cases of hypochromic microcytic anemia and of macrocytic anemia was treatment ever effective in increasing the blood count. In three cases of hypochromic microcytic anemia, one of which was associated with cirrhosis and two with malignant disease of the liver, iron therapy was definitely effective.

In four cases of macrocytic anemia, three of which were associated with cirrhosis and one with primary liver cell carcinoma, the intramuscular injection of liver extract was followed by a definite increase in the percentage of reticulocytes, a rise in the red cell count and a decrease in the mean corpuscular volume, such as occurs in pernicious anemia;[12] the reticulocyte response in patient E. K. R. (table 4) was associated with a temporary increase in mean corpuscular volume (fig. 1). In one patient who was given liver extract[13] orally and in three other patients with macrocytic anemia who were treated with liver extract administered intramuscularly, an increase in the number of erythrocytes and a decrease in mean corpuscular volume could less definitely be attributed to the therapy. A clearcut demonstration of the effectiveness of treatment could not have been expected in these cases, however, for the anemia was only moderate, the mean erythrocyte count being 3,960,000 as compared with an average count of 2,910,000 in the four cases in which treatment was definitely effective. In only one case of cirrhosis with macrocytic anemia was intramuscular liver therapy not followed by a decrease in the degree of anemia. The erythrocyte count in this case was 3,790,000, and the mean corpuscular volume, 97 cubic microns.

Since it has been shown that preparations of autolyzed yeast incubated with normal gastric juice are effective in causing a reticulocyte response in patients with pernicious anemia,[14] treatment with preparations of yeast was attempted in two cases of cirrhosis with macrocytic anemia and in one case of primary malignant disease of the liver with macrocytic anemia.

In one patient, whose gastric juice had already been shown to contain the "intrinsic factor,"[4a] the administration of a preparation of

12. Wintrobe, M. M.: Relation of Variations in Mean Corpuscular Volume to Number of Reticulocytes in Pernicious Anemia: The Significance of Increased Bone Marrow Activity in Determining the Mean Size of Red Corpuscles, J. Clin. Investigation **13**:669 (July) 1934.

13. Liver Extract-Lilly, N. N. R., was used.

14. Strauss, M. B., and Castle, W. B.: Nature of Extrinsic Factor of Deficiency State in Pernicious Anemia and in Related Macrocytic Anemias, New England J. Med. **207**:55 (July 7) 1932.

TABLE 4.—*Observations at Autopsy in Thirty-Four Cases of Hepatic Disease*

Patient	Diagnosis	Extent of Hepatic Damage, as Judged by†			Hematopoietic System*									
					Blood							Bone Marrow		
		Tests of Hepatic Function	Autopsy	Achlorhydria	Type of Anemia	R.B.C.	C.V.	C.C.	Smear I.E.	Spont. Rem.	Resp. to T.	Hyperplasia	Met.	Spleen H.F.
A. E.	Cirrhosis, biliary	..	++	..	None	4.66	87	34	0	..	..	+	0	++
L. B.	Cirrhosis, syphilitic	+++	+++	..	None	4.97	83	31	..	..	..	0	0	0
E. Sc.	Malignant disease, primary	+++	++++	..	None	5.95	85	30	0	+	..	+?	0	+++
M. S.	Malignant disease, primary	+++	++	+	None	4.30	88	32	..	..	..	0	0	0
W. B.	Malignant disease, secondary to that of pancreas	..	++++	+	None	5.06	99	32	+	0	..	+	+	++
C. G.	Malignant disease, secondary to that of stomach, and early nodular cirrhosis	..	++	+	None	5.24	86	31	..	..	..	+	0	0
R. E.	Acute yellow atrophy	..	++++	..	None	4.77	80	35	..	..	..	0	0	0
Q. S.	Acute yellow atrophy	..	++++	0	None	4.50	93	28	..	..	..	+	0	0
W. L.	Acute yellow atrophy	..	++++	..	None	6.07	86	31	0	..	..	0	0	0
V. B.	Acute yellow atrophy	..	++++	..	None	5.48	81	30	0	..	..	++	0	0
J. Bo.	Cirrhosis, biliary	++	++++	0	Macrocytic	2.50	103	..	..	..	..	++	0	+?
E. K. R.	Cirrhosis, biliary (Hanot)	+++	++++	0	Macrocytic	2.66	117	29	++	..	++	++	0	..
A. Z.	Cirrhosis, toxic	+++	++++	0	Macrocytic	3.64	102	36	+	+	+?	++	0	++
L. S.	Cirrhosis, toxic	..	++++	..	Macrocytic	3.11	106	31	+	..	..	+	0	..
R. P.	Cirrhosis, pigment	0	+++	0	Macrocytic	3.21	97	32	0	+	..	++	0	+
J. H.	Malignant disease, primary, and biliary cirrhosis	++	++++	0	Macrocytic	3.15	101	37	+?	..	++	+	0	..
J. C.	Malignant disease, primary, and biliary cirrhosis	..	++++	..	Macrocytic	2.60	100	..	..	..	..	+	0	+++
M. M.	Malignant disease, secondary to that of ascending colon, and slight biliary cirrhosis	..	++++	0	Macrocytic	3.25	96	30	+?	+?	..	++	0	++
M. C.	Malignant disease, secondary to that of gallbladder, and biliary cirrhosis	..	+++	+	Macrocytic	3.50	99	..	..	..	.	+	0?	+++
G. B.	Malignant disease, secondary to that of pancreas, and biliary cirrhosis	..	+++	..	Macrocytic	2.22	105	28	+	..	..	+	0	+
C. S.	Amyloidosis	..	+++	+	Macrocytic	2.48	106	33	+	+	..	+	0	..
P. E. B.	Cirrhosis, nodular	..	++	..	Normocytic	3.21	86	30	++	..	..	..	0	..
S. C.	Cirrhosis, nodular	+++	++	0	Normocytic	3.04	80	32	0	0	..	0	0	0
A. J.	Malignant disease, secondary to that of stomach	..	+	+	Normocytic	4.00	81	30	..	..	..	+	0	0
J. L.	Malignant disease, secondary to that of gallbladder	0	+	+	Normocytic	4.18	84	32	+	..	..	+	0	0
I. E.	Malignant disease, secondary to that of gallbladder	..	+	0	Normocytic	3.94	86	33	..	0	..	0	0	0
T. H.	Malignant disease, secondary to that of pancreas	..	+	..	Normocytic	4.45	87	31	0	..	..	0	0	0
E. So.	Malignant disease, secondary to that of pancreas	0	+++	0	Normocytic	4.41	80	34	0	..	..	+	+	+++
J. Bi.	Malignant disease, secondary to that of pancreas, and early biliary cirrhosis	..	++	0	Normocytic	2.71	91	36	..	..	..	0	0	..
A. T.	Malignant disease, secondary to that of lung	++	++	+	Normocytic	3.72	87	30	0	0	..	0	0	0
C. S.	Acute yellow atrophy	..	++++	..	Normocytic	4.18	89	34	..	..	..	0	0	0
L. S.	Malignant disease, secondary to that of stomach	..	++	..	Hypochromic microcytic	2.65	65	29	..	..	..	0	0	..
G. R.	Malignant disease, secondary to that of stomach, and slight biliary cirrhosis	..	++	+	Hypochromic microcytic	2.85	78	29	0	..	..	+	0	..
J. G.	Malignant disease, secondary to that of pancreas	..	++	..	Hypochromic microcytic	3.39	77	28	0	..	..	++	0	0

* R.B.C. indicates the number of red corpuscles in millions per cubic millimeter; C.V., mean corpuscular volume in cubic microns; C.C., corpuscular hemoglobin concentration in percentage; Smear I.E., evidence of increased erythropoiesis as indicated by anisocytosis, polychromatophilia, reticulocytosis or the presence of nucleated red corpuscles; Spont. Rem., spontaneous increase of erythrocyte count; Resp. to T., response to treatment; Met., metastases in bone; Spleen H.F., hematopoietic foci in spleen.

† The extent of damage is indicated by symbols as follows: slight, +; moderate, ++; extensive, +++; very extensive, ++++.

autolyzed yeast (Vegex), 1 ounce (28 Gm.) daily for nine days, was associated with a rise in the reticulocyte count from 0.6 per cent to 1.8 per cent on the fifth day after commencement of the treatment and an increase in the erythrocyte count from 4,080,000 to 4,260,000. The administration to another patient of yeast tablets,[14a] 6 daily, and of a preparation of purified wheat embryo (Embo) rich in vitamins B_1 and E and containing large amounts of vitamin A and G, 2 ounces

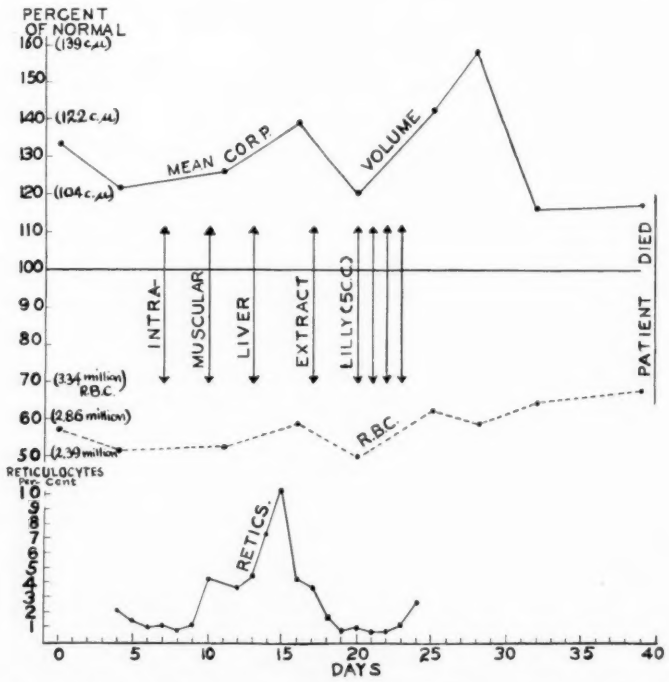

Fig. 1.—Effect of intramuscular injection of liver extract in a case of biliary cirrhosis with macrocytic anemia (E. K. R., table 4). The mean corpuscular volume and the number of red corpuscles are represented in proportion to the normal values, the ideal for both being 100 per cent. Reticulocyte counts were unfortunately not made after the twenty-fourth day, but the second temporary increase in mean corpuscular volume suggests that there was an added response to the last four intramuscular injections.

daily, was not followed by any changes in the blood. In the same patient, however, nine months later, when the anemia was more severe,

14a. Each tablet is said to contain "200 mg. of standardized vitamin fraction, according to Osborne and Wakeman" (J. Biol. Chem. **40**:383 [Dec.] 1919).

the administration of a specially prepared concentrate of vitamin B complex,[15] 24 Gm. daily for eleven days, was followed by a somewhat irregular increase in the number of reticulocytes, from 2 to 4.7 per cent, and an increase in the erythrocyte count from 3,410,000 to 3,920,000. The administration to a third patient of brewer's yeast, 9 tablets daily, was not followed by any changes in the percentage of reticulocytes or the erythrocyte count, but the latter was already 3,700,000 and had risen in response to intramuscular liver therapy.

Treatment with "secondary anemia" liver extract and iron was attempted in one case of cirrhosis with macrocytic anemia. An amount corresponding to 400 Gm. of liver and 2.6 Gm. of iron and ammonium citrate was given daily, but no change in the erythrocyte count (3,790,000) or in the percentage of reticulocytes followed. This is contrary to Cheney's experience,[4b]

TABLE 5.—*Relation of Extramedullary Hematopoiesis (Spleen) to Type of Anemia*

Diagnosis	Number of Cases	No Anemia	Anemia			
			Macrocytic	Normocytic	Simple Microcytic	Hypochromic Microcytic
Hepatic disease						
Cases with hematopoietic foci	11	3	7	1	0	0
Cases with no hematopoietic foci	15	7	0	7	0	1
Miscellaneous diseases						
Cases with hematopoietic foci	6	1	4	1	0	0
Cases with no hematopoietic foci	17	1	0	8	6	2

HISTOLOGY OF THE HEMATOPOIETIC ORGANS

Dr. Arnold Rich has called my attention to the occurrence of foci of extramedullary hematopoiesis in the spleens of some of the patients who died of hepatic disease. The following observations regarding the presence or absence of such foci were made by him without any knowledge of the type of anemia which had been present in the cases.

The foci observed were usually numerous and contained normoblasts, frequently macroblasts, and occasionally myeloid leukocytes, in groups of from 6 to 20 cells (fig. 2). Such nests of cells were found in the spleens of eleven patients and were absent in fifteen. The spleens of the eight remaining patients, data on whom are recorded in table 4, were unsatisfactory for examination because of autolysis.

In seven of the eleven cases of hepatic disease in which foci of extramedullary blood formation were observed at autopsy, the anemia had been of the macrocytic type (table 5). No anemia had been observed in three cases, but it is interesting to note that macrocytosis

15. This preparation was furnished by Mead Johnson and Company. It contained 600 Chick and Roscoe vitamin B complex units per ounce (28.35 Gm.).

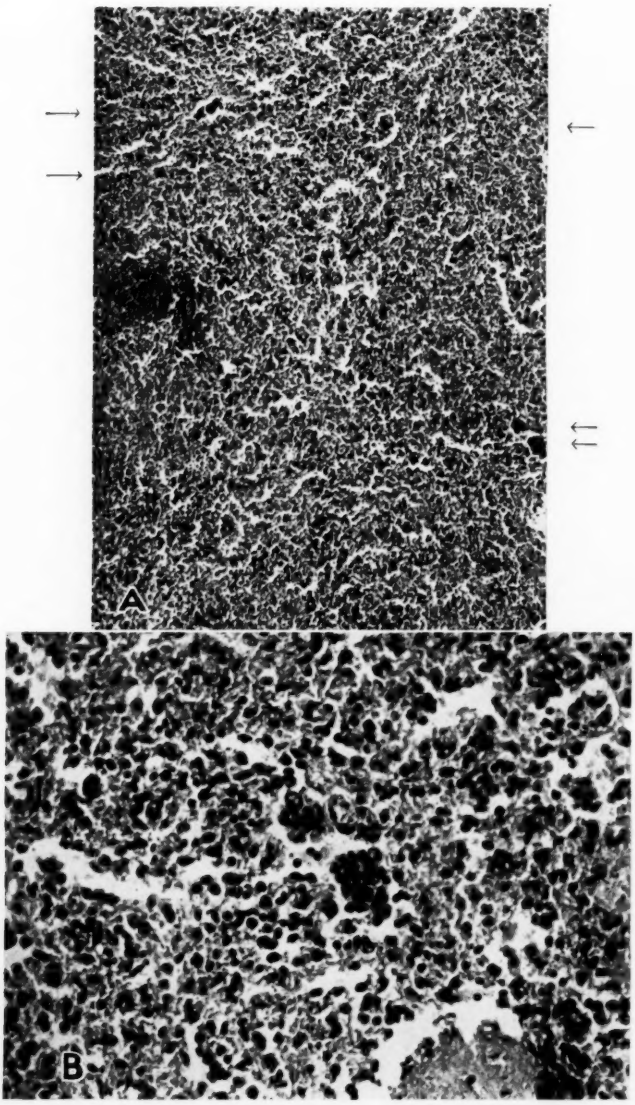

Fig. 2.—Foci of hematopoiesis in the spleen of a patient with metastatic carcinoma of the liver, biliary cirrhosis and macrocytic anemia (M. C., table 4). In *A* (low power magnification; × 100) the foci appear as small groups of deeply staining cells. In *B* one of the groups is shown in greater magnification (× 400).

(mean corpuscular volume 99 cubic microns) had been repeatedly found in one of the nonanemic patients (W. B., table 4). A metastatic nodule of tumor tissue was noted in a vertebra of one patient (E. So., table 4) in whom the anemia had been normocytic.

The high incidence of macrocytic anemia among the cases of hepatic disease in which extramedullary foci of blood formation were noted is in striking contrast to the complete absence of this type of anemia among the cases in which such foci were not observed (table 5).

For purposes of comparison, the spleens of twenty-three patients who had died of disease other than that of the liver in whose cases data concerning the type of anemia were available were examined. The diseases included pneumonia (three cases), nephritis (two), pellagra (two), hypophyseal cachexia and sepsis (one), aplastic anemia (three), benzene poisoning (one), sickle cell anemia (two), multiple myeloma (one), erythremia (one), pernicious anemia (three), multiple thromboses of the spleen (one), granulocytopenia (one), Hodgkin's disease (one) and carcinoma of the cervix (one). Examples of acute tumor of the spleen and of leukemia were excluded.

Foci of blood formation were observed in the spleens of six patients, one of whom had died of erythremia, one of Hodgkin's disease with widespread involvement of the bone marrow, three of pernicious anemia and one of multiple thromboses of the spleen. In the first there was no anemia, in the second there was normocytic anemia and in the other four the anemia had been macrocytic (table 5). In none of the remaining seventeen cases was extramedullary blood formation observed, nor had macrocytic anemia been found.

In all cases, then, both those of hepatic disease and the control group in which macrocytic anemia had been observed in association with other diseases, foci of hematopoiesis were noted in the spleen. In only two instances were the foci associated with any other type of anemia, but in four cases in which they were observed there had been no anemia.

In none of the cases were foci of blood formation observed in the liver.

An attempt has been made in table 4 to indicate the extent of blood formation in the bone marrow in the cases in which autopsy was performed. The estimate is based on the study of the femoral and vertebral bone marrow.

In all the cases of macrocytic anemia there was some evidence of increased blood formation in the femoral bone marrow. In five instances there was definite hyperplasia. On the other hand, although there was some indication of increased hematopoiesis in a few of the

cases of nonmacrocytic anemia, it was of no greater degree than in cases in which there was no anemia and was distinctly less than in the group of cases of macrocytic anemia. It is noteworthy that the cases of macrocytic anemia were, on the whole, little more severe than those of nonmacrocytic anemia.

RELATION OF MACROCYTIC ANEMIA TO TYPE OF HEPATIC DISEASE

A comparison of the data presented in tables 1, 2 and 3 indicates that macrocytic anemia was most commonly associated with cirrhosis of the liver. The relatively high incidence of macrocytic anemia in cases of cirrhosis becomes even more striking when the cases of hemolytic anemia and the cases in which the diagnosis of macrocytic anemia was doubtful are excluded, for then the incidence of macrocytic anemia in cases of cirrhosis becomes 36.6 per cent (15 cases), as compared with 16.1 per cent (five) in cases of malignant disease and 12.5 per cent (five) in cases of miscellaneous disorders of the liver. It is significant to note, moreover, that in all of the five cases of malignant disease of the liver in which macrocytic anemia occurred, cirrhosis of various degrees was associated with the malignant process. On the other hand, no instance of macrocytic anemia occurred among ten cases of malignant disease of the liver uncomplicated by cirrhosis.

RELATION OF EXTENT OF HEPATIC DAMAGE TO TYPE OF ANEMIA

The macroscopic and microscopic examinations of the liver in the cases in which autopsy was performed give the distinct impression that macrocytic anemia occurred in those cases in which damage to the liver was particularly great and extensively distributed. Such comments as the following by independent observers are typical: "Advanced cirrhosis . . . The whole process of scarring is finely and evenly distributed" (patient A. Z.); "the intervening liver tissue was seldom of wide enough extent to permit gaining an idea of the condition of the liver itself" (patient J. H.); "most extreme biliary cirrhosis" (patient G. B.); "the cirrhosis is diffuse and finely distributed so that individual cells are separated from one another by connective tissue" (patient E. K. R.). Furthermore, there was in these cases little or no regeneration of liver tissue.

In the cases of malignant disease in which macrocytic anemia was present, the regularity with which cirrhosis was associated with the malignant process further supports the impression that macrocytic anemia occurred in cases in which there was great damage to the liver. In the cases of malignant disease the total extent of destruction of the liver tissue was great indeed. On the other hand, in each of the three cases in which malignant disease was combined with cirrhosis (C. G.,

J. Bi., G. R.) and in which macrocytic anemia had *not* been noted, the cirrhosis was described as "early" or "slight" and the metastatic involvement was of only slight or moderate extent.

In table 4 an attempt has been made to indicate the extent of damage to the liver in each case, as judged by the postmortem examination and, in a few instances, as indicated by tests of hepatic function. Although the estimate of the extent of damage to the liver is admittedly only approximate, it serves to contrast the degree of damage in the cases of macrocytic and those of nonmacrocytic anemia. Of the eleven cases of macrocytic anemia, in seven the damage to the liver is designated according to postmortem observations as very extensive (++++), and in four, as moderately extensive (+++). Of the cases of nonmacrocytic anemia, in seven the damage is designated as very extensive; in two, as moderately extensive; in ten, as moderate (++), and in four, as slight (+).

It is also apparent from the study of these cases that if extensive damage to the liver leads to the development of macrocytic anemia, it is hepatic disease of long standing which is important. Of the five cases of acute yellow atrophy, although damage to the liver was extreme, no anemia was observed in four, and only slight, normocytic anemia was present in the fifth. It may be added that if the cases of acute hepatic disease are omitted, the number of cases of nonmacrocytic anemia with very extensive damage to the liver is reduced to two. It is interesting to note that in neither of these two cases had any anemia been observed but in one, macrocytosis was nevertheless repeatedly found.

COMMENT

The observations recorded indicate that in cases of hepatic disease, except when loss of blood or a complicating infection is present, anemia, when it develops, is either of the normocytic or of the macrocytic type. The macrocytic anemia observed is, in many respects, like pernicious anemia; although it is rarely as marked as the latter, it is morphologically similar, if not identical. Spontaneous remissions in the anemia may occur. Intramuscular liver therapy was followed in several cases by definite reticulocytosis and a decrease of anemia, such as occurs in cases of pernicious anemia.

In none of the cases was any clinical or postmortem evidence obtained which might have permitted the anemia to be attributed to any cause other than the hepatic disease or the associated malignant process. Achlorhydria was, in fact, less common (40 per cent) in cases in which macrocytic anemia was noted, than in the cases of nonmacrocytic anemia (64 per cent). Nor was any other cause of macrocytic anemia, such as acute loss of blood, discovered.

It seems to be a justifiable assumption, then, that the hepatic disease is the cause of the macrocytic anemia. In this connection it is important to emphasize that in the cases of macrocytic anemia the hepatic disease was of such long duration and was so widespread through the organ that little functioning liver tissue remained. Macrocytic anemia appears to be especially common in cases of cirrhosis of the liver, and in this disease the illness is characteristically chronic and the lesions widespread. In an earlier communication [4a] it was suggested that macrocytic anemia develops in a patient with hepatic disease as the result of faulty storage of the hematopoietic principle. There has been ample confirmation [16] of the experimental results of Richter, Ivy and Kim,[17] which first demonstrated that this principle is stored in the liver. Of further significance is Goldhamer's report [16b] that the liver of a patient who died of cirrhosis and macrocytic anemia was ineffective in the treatment of a patient with pernicious anemia whereas the liver of a patient who died of acute yellow atrophy contained the active hematopoietic principle. The evidence available at present suggests, then, that when damage to the liver is so extensive that storage is interfered with and when it has been of sufficient duration to permit exhaustion of the hematopoietic principle already present, macrocytic anemia develops.

There is no evidence to indicate that in the cases of hepatic disease there is any difficulty in utilizing the extrinsic factor from the diet or that the liver has any other function concerning the hematopoietic principle except that of simple storage. We have been able to demonstrate the presence of the intrinsic factor in the gastric juice of one patient with macrocytic anemia associated with hepatic disease.[4a] Unfortunately, the experiments already described, in which the effect on the blood of the oral administration of the extrinsic factor was studied, are not conclusive, but they tend to support the belief that patients with disease of the liver and macrocytic anemia are able to utilize the extrinsic factor to form hematopoietic principle. The ability to utilize the extrinsic factor may explain why in cases of hepatic disease with macrocytic anemia the anemia is rarely severe, and the consumption of various amounts of active hematopoietic principle may explain the fluctuations in the degree of anemia which have been so frequently observed.

The foci of blood formation observed in the spleens of the patients who had hepatic disease with macrocytic anemia are of considerable

16. (*a*) Wilkinson, J. F., and Klein, L.: The Haemopoietic Activity of the Normal and Abnormal Human Liver, Quart. J. Med. **3**:341 (July) 1934. (*b*) Goldhamer, S. M.; Isaacs, R., and Sturgis, C. S.: The Rôle of the Liver in Hematopoiesis, Am. J. M. Sc. **188**:193 (Aug.) 1934.

17. Richter, O.; Ivy, A. C., and Kim, M. S.: Action of Human "Pernicious Anemia Liver Extract," Proc. Soc. Exper. Biol. & Med. **29**:1093 (June) 1932.

interest because such foci have rarely been observed in adults except in cases of pernicious anemia, osteosclerosis and carcinomatous replacement of the bone marrow and in rare cases of sepsis. Meyer and Heineke [18] originally described small collections of normoblasts, myelocytes and lymphocyte-like cells in the spleens of seven patients who had pernicious anemia. They observed similar changes in the liver, but these were much less constant. Schridde [19] confirmed the findings. Myeloid metaplasia in the liver and spleen in cases of osteosclerosis and carcinomatosis of the bone marrow was first noted by Askanazy [20] and by Donhauser.[21] All of these observations have been confirmed,[22] and are generally quoted,[23] but there are few reports concerning the occurrence of extramedullary hematopoiesis in any other conditions in adults. Weil [24] described hematopoietic foci in the spleens of persons dying of various infectious diseases, especially variola, but in cases of the acute tumor of the spleen arising from infection myeloid metaplasia is extremely difficult to distinguish.[22a] Meyer and Heineke [18] found extramedullary blood formation in the spleen in two cases of secondary anemia of septic origin, and Schridde [19] also stated that it may occur, though rarely. Brannan [25] observed blood formation in the spleen, liver and broad ligaments of a woman who died of anemia and sepsis following incomplete abortion, and hematopoietic foci have even been observed developing in adipose tissue in cases of sepsis.[26] Meyer and Heineke [18] included among their patients showing extramedullary hematopoiesis one patient with "anemia with cardiac disease." Draper [27]

18. Meyer, Erich, and Heineke, Albert: Ueber Blutbildung in Milz und Leber bei schweren Anämien, Verhandl. d. deutsch. path. Gesellsch. **9**:224, 1905.

19. Schridde, H.: Ueber Regeneration des Blutes unter normalen und krankhaften Verhältnissen, Centralbl. f. allg. Path. u. path. Anat. **14**:865, 1908.

20. Askanazy, M.: Ueber extrauterine Bildung von Blutzellen in der Leber, Verhandl. d. deutsch. path. Gesellsch. **7**:58, 1904.

21. Donhauser, J. L.: The Human Spleen as an Haemoplastic Organ, as Exemplified in a Case of Splenomegaly with Sclerosis of the Bone-Marrow, J. Exper. Med. **10**:559, 1908.

22. (*a*) Rich, A. R.: Personal communication to the author. (*b*) Jordan, H. E.: Extramedullary Erythrocytopoiesis in Man, Arch. Path. **18**:1 (July) 1934.

23. Naegeli, O.: Blutkrankheiten und Blutdiagnostik, Berlin, Julius Springer, 1931, p. 127. Boyd, William: The Pathology of Internal Diseases, Philadelphia, Lea & Febiger, 1931, p. 564.

24. Weil, E.: Le sang et les réactions défensives de l'hématopoièse dans l'infection variolique, Paris, G. Steinheil, 1901; quoted by Brannan.[25]

25. Brannan, Dorsey: Extramedullary Hematopoiesis in Anemias, Bull. Johns Hopkins Hosp. **41**:104 (Aug.) 1927.

26. Petri, E.: Ueber Blutzellherde im Fettgewebe des Erwachsenen und ihre Bedeutung für die Neubildung der weissen und roten Lymphknoten, Virchows Arch. f. path. Anat. **258**:37, 1925.

27. Draper, George: Blood Formation in Liver and Spleen in Secondary Anaemias: Report of a Case, Bull. Ayer Clin. Lab., Pennsylvania Hosp. **6**:14, 1910.

observed many small nests of myelocytes throughout the spleen of a patient with severe anemia who died of chronic nephritis. Schridde [19] failed to observe extramedullary blood formation in cases of post-hemorrhagic anemia, either acute or chronic. It may be added that tumor-like growths of extramedullary hematopoietic tissue have been observed in several cases of hemolytic jaundice,[28] and actual heterotopia of the bone marrow [25] has been reported.

Among the cases of hepatic disease described here there were only two in which any of the conditions known to be associated with the development of extramedullary hematopoietic foci were discovered. In each of these cases one small vertebral metastasis was noted. A single metastasis can hardly be considered as an adequate stimulus for the development of extramedullary hematopoiesis, but it is possible that other bone metastases were present, which were not discovered. Be that as it may, there remain nine cases in which there was found no cause for the hematopoietic foci other than the hepatic disease. Certainly one could not attribute their formation to the development of severe anemia, for the anemia was little more severe in the cases in which hematopoietic foci were found than in those in which they were absent, the mean erythrocyte count for the former being 3,730,000 and for the latter 4,410,000.

Among the reports of cases of hepatic disease with macrocytic anemia which were reviewed in an earlier communication,[4a] only in the case of pigmentary cirrhosis reported by Bittorf was there mention of the observation of hematopoietic foci in the spleen. The failure to discover such foci is, however, probably of little significance, for they can be readily overlooked, as they were in the routine study in the majority of the cases of hepatic disease described here. In addition to Bittorf's observation, already mentioned, only two reports of cases of hepatic disease have been found in which myeloid changes in the spleen had been observed. Gandy and Bornait-Legueule [29] noted myeloid changes in the spleen of a patient with severe (possibly macrocytic) anemia who showed marked splenomegaly and pigmentation of the liver with beginning cirrhosis. Pissavy and Thibaut [30] described a patient with obstructive jaundice, hepatomegaly and splenomegaly and

28. Dawson, B. E.: Hume Lectures on Hemolytic Icterus, Brit. M. J. **1**:963 (June 6) 1931. Hunter, Donald: Personal communication to the author. Hartfall, S. J., and Stewart, M. J.: Massive Paravertebral Heterotopia of Bone Marrow in a Case of Acholuric Jaundice, J. Path. & Bact. **37**:455 (Nov.) 1933. Rich.[22a]

29. Gandy, C., and Bornait-Legueule: Anémie splénique: hyperplasie myéloïde de la rate; hemosidérose viscérale, Bull. et mém. Soc. méd. d. hôp. de Paris **23**:694, 1906.

30. Pissavy, A., and Thibaut: Anémie hépato-splénomégalique avec réaction hématopoïetique complexe, Bull. et mém. Soc. méd. d. hôp. de Paris **34**:813, 1912.

pronounced (macrocytic?) anemia. The anemia had been aggravated, if not largely caused, by repeated epistaxes. The liver at autopsy showed slight cirrhosis, and the spleen contained hematopoietic foci. Weil and Clerc [31] noted myeloid changes in the spleen in a group of twelve cases in which the condition was characterized clinically by distinct splenomegaly and severe anemia with marked normoblastosis and leukocytosis. The liver was increased in size in eight instances, but this was never a prominent symptom, nor were there signs of hepatic dysfunction. The cases are, therefore, probably not analogous to those discussed in this paper.

The presence of foci of extramedullary hematopoiesis in cases of chronic and widespread hepatic disease with macrocytic anemia is another point of similarity to pernicious anemia, in which, it has been already pointed out, blood formation in the spleen is common. When the similarity is considered in the light of the observations already recorded, it is reasonable to suspect that the development of extramedullary blood formation may occur in both instances as the result of the same fundamental abnormality, namely, a deficiency in a necessary hematopoietic principle.

Another analogy presents itself, which is concerned with the biologic significance of macrocytosis in general. This analogy is afforded by observing the regularity with which macrocytosis and extramedullary blood formation were associated in the cases studied, both in the group of cases of disease of the liver and in the control group, and by recalling the fact that macrocytosis is a characteristic of the blood of the fetus [32] and new-born infant, just as extramedullary hematopoiesis is normal at that period of life. It will be interesting to determine whether macrocytosis and extramedullary blood formation are consistently associated and whether or not they represent, in disease, a return to the type of blood formation characteristic of the fetus and the lower verebrates.

SUMMARY AND CONCLUSIONS

A study of the blood in one hundred and thirty two cases of hepatic disorder of various etiology is recorded. The postmortem observations in thirty-four of the cases are considered in relation to the type of anemia observed.

31. Weil, P. E., and Clerc, A.: De la splénomégalie chronique avec anémie et myélémie, Arch. gén. de méd. **8**:560, 1902.

32. Wintrobe, M. M., and Shumacker, H. B., Jr.: Comparison of Hematopoiesis in the Fetus and During Recovery from Pernicious Anemia, J. Clin. Investigation **14**:837 (Nov.) 1935; Erythrocyte Studies in the Mammalian Fetus and Newborn, Am. J. Anat. **58**: (March) 1936, to be published.

Except when hemorrhage or a complicating infection was associated with it, anemia associated with hepatic disease was either normocytic or macrocytic.

The macrocytic anemia was morphologically similar to if not identical with that seen in pernicious anemia. Like the latter, it manifested spontaneous remissions and was influenced by intramuscular liver therapy.

Macrocytic anemia was found in cases of hepatic disease of some duration and of wide extent. It was most common in cases of cirrhosis of the liver. It was not found in cases of acute necrosis of the liver or when the damage to the liver was only slight or moderate in severity.

Foci of blood formation in the spleen were observed in the cases of hepatic disease with macrocytic anemia as well as in association with other forms of macrocytic anemia, but, with two exceptions, they were not noted in association with any other type of anemia.

The observations recorded support the hypothesis that macrocytic anemia in cases of hepatic disease results from an inability to store a necessary hematopoietic principle.

NEURITIC MANIFESTATIONS IN DIABETES MELLITUS

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A man (case 9,009) of quiet and controlled temperament was brought in an ambulance to the hospital. He was moaning and writhing in pain, although his pupils were already contracted by morphine administered for an attack of suspected ureteral colic. A second patient (case 10,349), a former football player and coach, was admitted to the hospital because of such unaccountable depression, restlessness and severe burning sensations in his feet that he could not sleep. A third patient (case 10,405) was admitted because paralysis of the muscles of the foot had prevented his working for the preceding two months. A fourth patient (case 8,428), a man 30 years of age, was admitted to the hospital because of gangrene following a burn from an electric pad applied to a painful foot and lower part of the leg. All four suffered from diabetic neuritis. In 1864 Marchal de Calvi drew attention to the causal relationship between diabetes and disturbances of the nervous system, and in 1931 Wendt and Peck again emphasized diabetic neuritis. Sevringhaus (1931) reported diminished activity of the reflexes in 57.3 per cent of 75 diabetic patients studied for this condition, and Bolduan (1932) observed that 2 per cent of the population died of diabetes. Thus one sees that a large number of persons are afflicted with diabetic neuropathy.

HISTORY OF THE CONDITION

Early Observations.—In 1864, when Duménil was drawing attention to multiple neuritis and shortly after Bernard and his co-workers by their experiments had given such impetus to the consideration of lesions of the central nervous system as a cause of diabetes, Marchal de Calvi pointed out that diabetes may be the cause rather than the result of neurologic disturbances. Even prior to 1864, symptoms suggestive of diabetic neuropathy had been described.[1] As summed up by Auché (1890), the reports of the early writers,[2] from 1864 to 1884, dealt in a rather theoretical manner with the mechanism causing the nervous symptoms, which were described to a limited extent.

From the George F. Baker Clinic, Elliott P. Joslin, M.D., Medical Director, the New England Deaconess Hospital, Boston.

1. Rollo (1797). Frank (1842). Bardsley (1807). Billiard (1852).

2. Christi-Buici (1873). Worms (1880). Mary (1881). Raymond and Oulmont (1881). Berger (1882). Drasche (1882). Rosenstein (1882). Charrin and Guignard (1882). Bouchard (1882). Bernard and Féré (1882). Demange (1883). Barth (1883). Dreyfous (1883). Dieulafoy (1884). Cornillon (1884).

Later Observations.—According to Charcot (1890), Bouchard presented in a lecture in 1881 his observation that the knee jerks are often absent in diabetic persons; he published this report in 1884. Marinian in the same year published a similar report, and, according to Woltman and Wilder (1929) and Wright (1931), Althaus also recognized this pseudotabes of diabetes in 1884. From then until 1910 the literature concerning diabetic neuropathy increased rapidly. Since 1910 sporadic descriptions have appeared, one of the most notable, other than those in such comprehensive books as Joslin's (1928) and von Noorden and Isaac's (1927), being that by Woltman and Wilder (1929). After Bouchard's paper appeared, reports of the signs, as well as of the symptoms, became more numerous. Pryce (1887) described a sluggish pupillary reaction and ataxia, the latter of which was also mentioned by Pavy (1887) and von Leyden (1888). Von Leyden, who in 1880 had stimulated interest in nonspecific multiple neuritis, in 1888 reported cases of diabetes with paralysis and separated diabetic neuritis into three groups: the hyperesthetic, the paralytic and the ataxic. Von Ziemssen (1885) attributed the neuralgia of diabetes to peripheral neuritis but gave no pathologic proof. Von Hösslin (1886) commented on the absence of paralysis in diabetic persons with neuralgia; but in 1890 typical cases of diabetes with paralysis were reported by Althaus, Auché, Buzzard and Charcot. The case reported by Althaus was one of mononeuritis of the circumflex nerve, with atrophy of the muscles. Trophic ulcers were present in a case reported by Pryce (1887) and in one recorded by Buzzard (1890); and Raven (1887) reported a case with associated atrophy of the optic disk. Auché (1890), in a good article, summed up the literature and stated that the nervous complications of diabetes may involve all nerve functions: motor, sensory, special sensory, intellectual and nutritional. He listed among the symptoms pain especially at night, deep pain, lancinating and lightning pain, paresthesia, hyperesthesia, anesthesia, tenderness of nerves, changes in the reflexes, paralysis and vasomotor and trophic difficulties. He did not think that there was involvement of the bladder and rectum. He believed that this form of neuritis was not rare in diabetes, and he compared it with alcoholic neuritis, which had been done by von Leyden (1888), Minor (1889), Charcot (1890) and Buzzard (1890). Thus one sees that by 1890 the clinical picture of diabetic neuritis was rather complete.

Since 1890, many phases of diabetic neuritis have been described. Williamson wrote several articles. Lépine (1909), Labbé (1922), von Noorden and Isaacs (1927) and Joslin (1928) devoted sections in their books to the subject. Woltman and Wilder (1929) wrote a comprehensive paper, especially on the pathologic process, and Root and Rogers (1930) reported 11 cases with associated paralysis.

OBSERVATIONS

Selection of Cases.—The cases described here were selected from those of patients treated at the Joslin Diabetic Clinic in 1930, 1931 and 1932. Cases were chosen in which the symptoms and signs suggestive of neurologic disturbance were not obviously due to conditions other than diabetes. At first only cases generally designated as instances of neuritis were taken; but later, as it became evident that the condition in these cases blended into other somewhat similar conditions, cases of other types of neuropathy were observed so that the significance and the relation of the conditions to neuritis proper might be studied.

Grouping of Types of Cases.—I have divided the series of cases into four groups, according to the nature of the manifestations: (1) hyperglycemic type, 34 cases; (2) circulatory type, 27 cases; (3) degenerative type, 45 cases, and (4) neuritic type, 120 cases. This classification was made not to establish a new nomenclature but purely for the purpose of this study. The term diabetic neuritis has gained significance, however vague, through long usage, and it conveys meaning to physicians in many countries. 1. The first group comprises cases in which neuritic symptoms (usually with no signs other than tenderness of the nerve or muscles affected) were associated with an abnormally high sugar content of the blood, disappeared within a few days after the initiation of adequate diabetic treatment and did not recur if the diabetic regimen was followed. 2. The second group includes those cases in which there was considerable circulatory deficiency in the legs and, in addition, pain, paresthesia or signs such as hyporeflexia and hypesthesia. 3. The third group is composed of cases in which rather mild neuritic symptoms and signs began insidiously and tended to progress slowly over a period of years. This group includes cases with such findings as sluggish pupillary reactions and hyporeflexia. Occasionally the neuropathy involved structures which by their nature drew attention to them, as in cases of involvement of the bladder. 4. The fourth group embraces the cases in which there were definite manifestations of neuritis, usually with relatively severe symptoms or signs, such as paralysis. The onset was relatively acute, and improvement usually took place within a few weeks or months.

1. HYPERGLYCEMIC TYPE

Thirty-four cases of the hyperglycemic type are reported on here. No attempt was made to include all those cases observed during the thirty-two months of this study. The cases were selected at random from those encountered. They seemed to show the various features of the condition and to be fairly representative of the group as a whole. The cases were segregated because there were neuritic symptoms (with

no signs of neuritis except tenderness), which disappeared simultaneously with the reduction of the glycosuria. In 2 of the 34 cases the diabetes was controlled with great difficulty, and it was a matter of months before it was well regulated and the symptoms were relieved. In these 2 cases there were other features that rendered them a little atypical. In 1 (case 5,932) the patient had pulmonary tuberculosis, and signs of neuritis developed about the time the pain disappeared. In the second case (case 6,659) pain and tenderness of various nerves and muscles developed immediately after the extraction of an abscessed tooth, with an exacerbation of symptoms after the extraction of a second abscessed tooth; and the patient did not become symptom-free until five months after the second episode. Incidentally, the neuritis became much worse when pills of ferrous carbonate were given, possibly owing to constipation. In both of these cases the patient was young and had severe diabetes. Even with treatment there were hyperglycemia and glycosuria; so it is not surprising that pain persisted so long.

Site, Symptoms and Signs.—The site of this type of neuritis[3] varied little. In 26 cases (76.5 per cent) it involved only the legs. In the other 8 cases, there was more or less generalized involvement, either of the arms and legs together or of the entire body. The outstanding symptom was pain, especially at night when the patient was in bed. Some patients had pain only at night, and in most instances relief followed pacing the floor. Cramps, again especially at night, were at times the outstanding symptom. Sometimes the pain was transitory and sharp, and at other times, merely a dull ache. Once it was described as "a tearing of the calf muscles." This nocturnal type of pain is often referred to circulatory deficiency, but that did not seem to be true in these cases. At least, there was no obvious circulatory deficiency, and many of the patients were young and had little if any arteriosclerosis. Sometimes only paresthesia was present. This was manifested by coldness, numbness or prickling. Hyperesthesia to touch has been noted, as has a sensation of weakness, although I did not observe muscular paresis in any case. Some patients became nervous, irritable or depressed, but only 1 patient (case 6,659) showed a definite psychic upset. Tenderness of the nerves and muscles was not infrequently noted, and in some instances there was hyperesthesia. In 1 case (case 10,416) there was hypesthesia of the left side of the body, with no other evidence of cerebral vascular accident. Paresthesia of the left side of the body had been present for the six months during which the patient had had diabetes, and yet it disappeared on the second day after diabetic treatment was started. A decrease of the tendon jerks was noted in 5 cases, in each of which there was a combination of two or more of

3. For convenience I shall refer to each type as neuritis.

the types described. In each of these cases symptoms were relieved at once by diabetic treatment.

Fever and Blood Picture.—A tabulation of the temperature was not made for this group, although routine readings of temperature were noted for each patient, no one of whom had a noticeable febrile reaction not accounted for by other conditions. A white blood cell count was made in 6 cases, and the values ranged from 6,450 to 10,350. In 5 cases a blood smear was made. In 1 of these cases there was an abnormality, presumably due to an acute pulmonary infection of which the patient died in a few days. In another case (case 10,945) there was 7 per cent eosinophilia without known cause. In the other 3 cases smears were normal.

Pathology.—Prompt recovery prevented a study of the pathologic process.

Etiology.—Discussion of the etiology of each type separately necessitated considerable repetition, but it seems worth while as an aid in determining the various factors at work.

Sex and Age: Of the 34 patients, 23 were women and 11 (32.4 per cent) men. The age at the onset of the neuritis varied from 18 to 70 years, with an average of 46.4 years. Nine patients (26.5 per cent) were less than 40 years old, and 7 (20.6 per cent) were below 30 years of age.

Severity and Duration of the Diabetes: The diabetes was not always severe, but at the time symptoms appeared it was always uncontrolled. In 10 cases (29.4 per cent) the diabetes was mild, and in only 3 (8.8 per cent) was it severe. Thus, one sees that even though a diabetic patient has considerable glycosuria and neuritic pain, by adhering to treatment he may be relieved of the pain within a few days and may prove to have mild diabetes, requiring little or no insulin. Several of the patients had symptoms of neuritis before the apparent onset of the diabetes. This is not surprising, since marked hyperglycemia and glycosuria are often unassociated with hunger, thirst and polyuria. Two of the patients had had diabetes for thirteen years before neuritis began. The average duration of the diabetes prior to the appearance of neuritis was three and three-tenths years.

Dehydration and Acidosis: The clinical appearance of the patient or a gain of several pounds in weight within the first few days of treatment was used as a measure for dehydration. By this standard it was noted that dehydration was present in 10 cases (29.4 per cent). Furthermore, as judged by the clinical appearance of the patient or the finding of acetone bodies in the urine, acidosis was present in only 9 cases (29.5 per cent). In 22 cases (64.1 per cent) there was neither dehydration nor acidosis. Such evidence suggests that neither of these

factors is essential for the production of the symptoms. Furthermore, it is well known that whereas in many cases diabetic coma is accompanied by severe pain, in others there is none, even though acidosis and dehydration are marked. Recently I closely questioned 9 diabetic patients with marked dehydration, 4 of whom had definite acidosis (in 2 the carbon dioxide-combining power of the plasma was below 20 volumes per cent), and none had the slightest symptom of neuritis.

Cholesteremia: I used the cholesterol content of the blood as an index of the disturbance of fat metabolism, especially in the patients without acidosis. Such an analysis was made on 13 of the patients, 6 (46.2 per cent) of whom had hypercholesteremia. Such a percentage is not high, for in all these patients the diabetes was uncontrolled. The lowest cholesterol value was 145 mg.; the highest, 305 mg. (230 mg. being the maximum of normal), and the average, 225 mg. Two factors tend to exclude hypercholesteremia as a cause of the symptoms. First, more than half the patients tested showed normal cholesterol values. Second, the level of cholesterol in the blood changes slowly under the treatment at the clinic, and these patients obtained relief within a few days after treatment was instituted.

Accessory or Nondiabetic Factors: Foci of infection were present in 25 per cent of the cases, but relief from the symptoms was not postponed until the infection was removed. Arteriosclerosis is so prevalent in diabetic persons that its high incidence is not significant. In 6 cases (17.77 per cent) there was no arteriosclerosis, and in 3 others there was only a slight degree of it. A previous dietary deficiency had not existed in the 5 cases in which there was specific questioning about this. Achlorhydria was present in only 2 of the 10 cases in which a test was made, and in these 2 there was no other evidence of pernicious anemia or combined system disease. Tuberculosis was present in only 1 case. The prompt relief of symptoms tends to exclude all these factors as causative agents. No other possible causes were discovered.

I cannot say that hyperglycemia alone causes the symptoms, for it is often present in diabetic persons who have no symptoms and whose immunity is unexplained. Nevertheless it was the only factor noted in all cases, and correction of it was followed immediately by a disappearance of the neuritic symptoms. Furthermore, it is recognized that in diabetic persons pain of a different nature from that described here is often worse when the value for blood sugar is high and less severe when the diabetes is controlled.

Prognosis.—The criteria for the selection of these cases necessitated a good prognosis. However, it is interesting to note that several patients who had had symptoms for more than a year obtained prompt relief when diabetic treatment was instituted. One patient (case 10,562) had had pains and cramps in the calves of the legs for the preceding seven

years, and yet twenty-four hours after the excretion of sugar in the urine decreased below 1 per cent all the symptoms stopped. In another patient (case 11,036) the right ankle jerk, which had been sluggish, became definitely more active within three days after the patient became aglycosuric. In all but 2 of the cases the diabetes was fairly easily controlled, and in only these 2 was relief from the pain delayed. In 31 of the 34 cases the symptoms disappeared within a week after the initiation of diabetic treatment. One patient (case 11,092) was not so fortunate, as his symptoms lasted sixteen days, but he had a carbuncle and considerable diabetic acidosis. The average duration of symptoms after treatment was begun was three and six-tenths days. The future course of these patients should prove interesting and instructive. Sufficient time has not elapsed for me to say what this hyperglycemic pain may signify. However, 4 patients have subsequently shown evidence of real neurologic disorder. One patient (case 9,913) nine years after the first attack of hyperglycemic symptoms had advanced circulatory deficiency of the legs, and there was absence of the tendon reflexes. Another (case 5,932), a boy of 18 years, although essentially symptom-free, had sluggishness of the knee jerks and right ankle jerk and absence of the left ankle jerk. Sensitivity to pinprick diminished on the anteromedial surface of the lower portion of the legs. Another patient (case 9,759) had neuritis with definite signs, although she had been aglycosuric and had been receiving insulin during the interim between the disappearance of the hyperglycemic symptoms and the onset of the neuritis. Incidentally, during the same period the pulsation in the dorsalis pedis arteries diminished practically to the point of absence. Another patient (case 9,765) experienced an almost identical course, including the circulatory change, in a period of ten months. The relatively slight increase in the duration of the diabetes in the 3 last mentioned cases is hardly sufficient to explain the changes.

Treatment.—The treatment was the regular regimen for diabetes. Relief is so prompt that other treatment is usually unnecessary. Heat, salicylates or hypnotics may be used if necessary. Massage was very effective in 1 case (case 6,659). The general condition of the patient and foci of infection should be given the attention required.

2. CIRCULATORY TYPE

To study this type, I have taken at random 27 cases. The frequency of the condition is illustrated by the large percentage of diabetic persons who have sufficient circulatory deficiency to warrant amputation of the legs. Labbé (1931) mentioned certain symptoms and signs observed in this condition.

One can quickly dispose of this type by stating that in all essential features it resembles the degenerative type. The onset, symptoms and

signs, course, site, etiology, age at onset, prognosis and treatment are the same in both groups, with few exceptions. The patients with circulatory deficiency occasionally have intermittent claudication, which was not present in the patients with the other type of neuritis. Parts of the body with no evident circulatory deficiency were affected in patients in this group, and those with degenerative nerve lesions in other parts of the body occasionally had sluggish circulation of the lower part of the legs. I believe that a separation of these two types is not indicated, that they should be grouped as one under the degenerative type. Provision for poor circulation of the feet can be made easily by prescription of Buerger's exercises and more careful attention to the feet to prevent and treat lesions which might receive surgical intervention. I shall therefore combine pertinent data on these 27 cases with those of the degenerative type.

3. DEGENERATIVE TYPE

Of the many cases of this type encountered I have used 45 for this study. Among these are cases illustrating the various features of this type of neuritis and also cases which disclose the difficulty of segregating some cases of this type from those of the hyperglycemic and neuritic types. These cases represent the type of neuropathy from which such a large percentage of diabetic persons suffer. They include the type of cases in which the routine examination discloses hyporeflexia or areflexia of the tendons or sluggish reactions of the pupils. Mild pain or paresthesia is usually acknowledged if one questions the patient, but the symptoms of neuritis are rarely a major complaint. The onset is insidious and the course prolonged. The supervention of other conditions may complicate the picture, so that a decision as to the type of neuropathy is reached with difficulty.

The earlier symptoms in case 8,166 suggested that the patient might have had real neuritis, but at the time of examination the mildness of the symptoms, the minor signs and the ten years' duration of the neuritis suggested rather a degenerative condition.

Site and Symptoms.—In 18 cases (40 per cent) there was involvement only of the legs; in 6 cases, of the arms and legs alone; in 10, of the pupils and legs, and in 2, of the pupils alone. In the remaining 9, there was generalized involvement. The predominant symptoms were pain, cramps and paresthesia. All symptoms were worse at night, usually markedly so, and were increased occasionally with fatigue. The pain was at times dull and at other times sharp, steady or momentary. Burning pains were complained of less among this group than among those with the circulatory type. One patient (case 10,100), in addition to neuritis of the leg, with a sense of vibration and a sensation as of "cold water poured down the bone," complained of neuralgia of the gums of two years' duration. The left pupil reacted sluggishly to light. Another

patient complained of a binding feeling around the calf, especially at night, so severe that he could not lie still. Fifty-seven and one-tenth per cent of the patients had pain of some type, and 55.3 per cent had paresthesias. The paresthesias included numbness, prickling, burning, coldness and, rarely, generalized itching. One troublesome and unexplained symptom, occurring in case 9,643, was numbness, as if the hands and feet were asleep. There were no other symptoms; and the only sign was absence of the knee jerks, although the ankle jerks were normal. There was no obvious circulatory deficiency or anemic condition. The gastric free hydrochloric acid showed 64 degrees of acidity. There was moderately advanced arteriosclerosis. In case 11,075 there was intractable numbness of the hands. There were also pain and tenderness of one arm and rectal incontinence, apparently dependent on a relaxed sphincter. In case 6,331 there were slight urinary incontinence and absence of the right ankle jerk. The cases in which there was loss of control of the sphincter will be discussed later.

Signs.—The neurologic observations included sluggishness or absence of the tendon jerks, weakness of the legs or of isolated groups of muscles with or without atrophy, weakness of the anal sphincter, tenderness of the nerves and muscles, hypesthesia, anesthesia, an abnormal pupillary reaction and, in 1 case, a positive Romberg sign. The hypesthesia was noteworthy. In 1 case in which there were no symptoms there was generalized hypesthesia, most marked on the lower portion of the left leg, and there were sluggishness of the left ankle jerk and absence of the right ankle jerk. One patient (case 10,528) did not show a noticeable decrease in sensitivity to pinprick, but she experienced almost no pain when the surgeon cut and probed the infected foot. The signs in 1 case were so striking, albeit rare, that I report it as follows:

CASE 10,451.—A 56 year old woman, with moderate arteriosclerosis and diabetes of fourteen years' duration, noted paralysis of the muscles elevating the foot. The ankle joint became swollen but not tender. Bits of bone were painlessly extruded from the toes. The lesions would heal but recur, or new ones would develop. The ankle joint became useless and instable. The process then involved the other ankle and foot. One ankle improved, the cutaneous lesions healed, and the foot drop became less noticeable. Two years after the onset I observed a rather typical, painless Charcot joint of the ankle, in addition to chronic osteomyelitis of the foot of an unusual type and without obvious etiology. There was partial left foot drop, with hypesthesia of the lower portion of the legs, most marked in the distribution of the external peroneal nerve. The knee jerks were normal, but there was absence of ankle jerks. The Wassermann test of the blood and spinal fluid gave negative results, but the colloidal gold curve resembled the type associated with dementia paralytica. Leprosy seemed an unlikely cause. The similarity of the disturbances produced by syphilis and diabetes and the absence of proof of the former in the history, the physical examination and the serologic study led me to consider this tentatively as a diabetic process of a neurologic trophic nature.

In 13 (28.9 per cent) of the 45 cases the knee jerks were normal; in 8 (17.8 per cent) there was absence of the patellar reflexes, and in 24 (53.3 per cent) there was absence of one or sluggishness of one or both reflexes. The ankle jerks were normal in only 7.3 per cent of 41 cases, and in these 3 cases there were other definite signs. Sensitivity to pinprick was normal in 55.6 per cent of 27 cases and decreased in the remaining 44.4 per cent. Sensation to touch, heat and cold corresponded to sensitivity to pinprick in the cases tested, but these tests were not employed frequently. In general, sensitivity, when abnormal, decreased progressively from the thighs down to the feet; but usually the distribution was patchy, so that one might strike sensitive points in areas otherwise insensitive. In case 5,112 there was sudden numbness of the dorsum of the left foot, with loss of sensation of pain and light touch. The pulsation in the dorsalis pedis artery was questionable. The following day the pulse was felt, and sensation was normal. I believe that sensitivity decreases with decreasing circulation and increasing arteriosclerosis, although there are a number of exceptions to this rule. Position sense of the great toe was tested in 25 cases and was decreased in only 3.

Pathology.—The pathologic process was not studied in these cases. Many of the cases reported in the literature seem to fall in this group of the degenerative type, and I shall mention here the pathologic process described in the literature. Changes were noted in the spinal cord by nine authors,[4] in the cord and nerves by eight,[5] in the peripheral nerves by eight[6] and in the posterior roots by three.[7] The early report and summary by Auché (1890) and the recent one by Woltman and Wilder (1929) are good. In the latter article are transcribed the histories of 42 cases reported in the literature, in 24 of which there was degeneration of the peripheral nerves, in 16 degeneration of the funiculi, in 8 changes in the anterior horn and in 4 intramedullary degeneration of the posterior roots. Auché described a case of parenchymatous neuritis with considerable myelin degeneration and changes in the axis-cylinder in isolated nerve fibers. The process seemed chronic and progressive, involving first one fiber and then another, the first affected often showing sufficient

4. Minor (1889). Lichtheim (Sandmeyer, 1892). Williamson (1898; 1904). Van Leyden and Goldscheider (1895). Nonne (1896). Souques and Marinesco (1897). Naunyn (1906). Schweiger (1907). Root and Rogers (1930).

5. Leichtentritt (1893). Van Leyden (1893). Bonardi (1897). Findlay (1902). Ossokine (1902). Bramwell (1907). Marinesco (1901). Woltman and Wilder (1929). In the last two reports chief stress was laid on lesions of the peripheral nerves.

6. Pryce (1887; 1893). Nonne (1889). Auché (1890). Eichhorst (1892). Fraser and Bruce (1895; 1896). Hensay (1897). Fleming (1897). Wittmaack (1907).

7. Williamson (1904; 1924). Hensay (1897). Schweiger (1907). According to Wright (1931).

regeneration so that the function of the nerve seemed never to be lost. Auché noted normal nerve tissue proximal to markedly diseased nerve tissue and concluded that the changes in the nerve were not secondary to changes in the spinal cord. Pryce (1893) was struck by the association of arterial disease with the degeneration in the nerves. Marinesco (1901) also commented on the thickening of the walls of the intraneural arteries. Woltman and Wilder (1929) noted slight changes in the cord and marked changes in the nerves. These changes consisted of patchy degeneration of the nerves, with myelin disintegration and at times infiltration by lymphocytes, polymorphonuclears and fat-laden cells. The lesions were more marked in the peripheral than in the proximal parts of the nerves, an observation described also by Auché. Woltman and Wilder noted sclerosis of the intraneural vessels and concluded that this arteriosclerosis was a most important etiologic agent. In 1 of their cases regenerated fibers were observed. Similar regeneration was reported by Nicolescu and Raileanu (1926; 1927) in their description of the pathologic changes in the brain in diabetes. Warren (1930) studied the pathologic process in many diabetic patients, a large number of his nerve specimens having been obtained from limbs amputated because of diabetic gangrene. The pathologic process in the nerves was not very conspicuous, but the small peripheral branches of the nerves were not studied. Sclerosis of the intraneural arterioles and occasionally myelin degeneration were observed.

Etiology.—Sex and Age: Two thirds of the patients were women, and this may be explained by the fact that the women were more nervous and probably drew attention to their neuropathy more often than did the men. The age at the onset of the neuritis varied from 40 to 77 years, with an average of 59.2 years. In the cases of the circulatory type the average age was 58.1 years, and the youngest patient was 40 years old.

Diabetic Factors: In this group the average duration of the diabetes before the onset of the neuritis was four and five-tenths years, but sometimes the neuritic symptoms preceded the apparent onset of the diabetes. In 6 cases the average duration of the neuritis prior to the diabetes was four and five-tenths years. The record for case 10,582 is interesting. The patient was admitted to the hospital with an occluded femoral artery and a neuritic condition of the diabetic type. However, throughout the first stay at the hospital tests of the urine and blood did not reveal evidence of diabetes, and my associates and I concluded that the neuritis, which we had thought rather characteristic of diabetes, was of a different etiology. Within a short time the patient returned with an inflammatory condition of the foot, and under this added strain the diabetic condition became evident, with a blood sugar content of 0.23 per cent. This patient had had neuritis for twelve years before the presence of diabetes was proved, although slight glycosuria had been noted previously. One may

contrast this with case 5,866 in which diabetes was present for twenty-four years before the neuritis was noted. In 18 cases (41.9 per cent) diabetes had been present for one year or less. Thus, there is no evidence to prove that long continued diabetes is necessary for the production of these nervous changes. The diabetes was mild in 31 cases (68.9 per cent) and severe in 3. Similarly, in 69.7 per cent of the cases the diabetes had previously been at least fairly well controlled, as judged by the tests of the urine cited by the patients. The values for cholesterol in the blood were not so good, as illustrated by the fact that in 7 of the 13 cases in which tests were made the values were above the maximum normal level, the average for the 13 cases being 236 mg. In the cases of the circulatory type the average value for cholesterol in the blood in 9 cases was 267 mg., which is 16.1 per cent above the maximum normal value.

Arteriosclerosis: By examination of the arteries I detected moderate or advanced arteriosclerosis in 41 of the 44 cases in which there was a record of this condition, and in 1 other a condition of the foot required surgical intervention, which in diabetic persons usually implies at least moderate vascular disease. Angina pectoris was present in 7 cases (15.6 per cent), a condition of the feet requiring surgical intervention in 19 (42.2 per cent) and apoplexy in 4 (in 1 of which it was questionable). The circulation in the legs seemed normal in only 20 per cent of the patients, and it was very deficient in 35 per cent. Of the entire group arteriosclerosis was present in every case, and in 95.5 per cent there was evidence of moderate or advanced vascular disease.

Dietary Deficiency: Fourteen patients questioned about their diets prior to the neuritis gave no history of a definite deficiency, although 1 patient (case 10,582) might not have eaten as much meat, fresh fruit and green vegetables as is usually considered normal. No deficiency of the nature of pernicious anemia was detected, although achlorhydria was present in 5 of 11 patients tested. Of the other 6 patients, only 1 had less than 25 degrees of free acidity, and the average for the 11 patients was 30.5 degrees. Among the patients with the circulatory type, only 1 of 7 tested had achlorhydria.

Alcohol, Foci of Infection and Syphilis: Of the 41 patients for whom there was a record of the consumption of alcohol, only 3 (7.3 per cent) had imbibed any. The incidence of foci of infection was also slight (11.6 per cent), but it is to be remembered that in many cases abscessed teeth may have been removed prior to my examination. Syphilis was present in none of the 45 cases.

To summarize the etiologic data, I may say that the only two factors, primary or contributary, which I have observed are the diabetes and the vascular disease. It seems that some obscure feature of the diabetes,

and not simply hyperglycemia, is at fault. The abnormality in the cholesterol content of the blood suggests a possible factor in the production of this neuropathy.

Prognosis.—The chronic and at times progressive nature of the condition precludes a good prognosis. The signs are likely to remain, if not to progress, in spite of the best treatment; and even the symptoms linger for months or years, although they may at times decrease considerably in severity. In some patients in whom the diabetes has been inadequately controlled relief from symptoms is moderate and rather prompt when they adhere to the diabetic treatment. Nine patients received relief in this manner, although in 4 the alleviation was slight. Two patients always paid by an increase in symptoms for any relapse in treatment. Amputation on account of markedly deficient circulation ended the symptoms in 1 case, but the absence of the knee jerk in the remaining leg testifies to the presence of the neuropathy. One patient received much benefit from Buerger's exercises. One patient (case 8,965) wrote that after two and one-half years she has had no more neuritis, and another (case 9,860) was relieved in one year; but in neither instance have I been able to examine the patient to see if the absence of the tendon jerks and other signs have been restored to a normal state. In case 1,217 the symptoms began when the patient was aglycosuric, according to her, and progressed during the three years prior to the time I saw her; yet rest and heat afforded relief. In 3 cases the neuritis has lasted ten years or more. One of these (case 8,166) is interesting. The manifestations of neuritis consisted of pain, paresthesia, weakness and areflexia in the legs. During the past several years the carbohydrate content of the diet has been gradually increased. In the past three years the neuritis has improved definitely. The symptoms and weakness disappeared, and the patellar reflexes have returned to the point where both can be obtained without reenforcement, and this in spite of hyperglycemia and a cholesterol value 41 per cent above the maximum normal. In case 10,135 there was also a lessening of signs. In a period of ten months during which the patient was treated with insulin, one knee jerk, which had been very sluggish, became practically normal and the paresthesia ceased. In case 9,643 there was absence of knee jerks, which later were partially regained. In case 6,331 there was absence of the ankle jerk on the right side but a normal ankle jerk on the left, the side on which there was hemiplegia. The average duration of the neuritis in the 45 cases has been three and five-tenths years. In the group of the circulatory type improvement in tendon jerks was noted in 3 cases (cases 1,696, 2,843 and 9,287). The average duration of the neuritis in this group was four and four-tenths years. Obviously this short duration is due at least partially to the fact that in general the patients have been observed over a period of only two and one-half years or less and

some were observed for the first time only a few months before this study was completed.

Treatment.—Persistent treatment of the diabetes should be demanded. One should not expect too much, because in 69.7 per cent of these cases the neuritis has appeared or persisted in spite of apparently well controlled diabetes. However, in a number of cases quite a little relief was obtained after the institution of diabetic treatment. Observation of roentgenograms of the legs of some diabetic patients makes one both discouraged and hopeful. The calcification of the arteries is often extreme and completely obliterates the lumen, but at the same time one sees evidence of smaller collateral arteries developing to care for the area formerly deprived of its blood supply. Buerger's exercises have given fairly good results in some cases and should be tried. In 19 of the cases of the circulatory type I know the effect of these exercises. Five patients obtained much relief, and 8, moderate relief, a total of 68.4 per cent. Only 3 patients failed to receive apparent benefit. Even these patients should continue the exercises, because in time sufficient collateral circulation may develop. Sedative measures, similar to those used for hyperglycemic symptoms, may be employed for the temporary relief of pain, but one must be more careful in prescribing drugs, because the condition persists for a long period. Furthermore, the vascular disease, with hypesthesia and susceptibility of the tissues to injury, makes it essential that extreme care be used in applying heat. In the hospital I have used an electric baker, regulated by a nurse who understands both the apparatus and the condition of the patient. Warm baths are sometimes recommended for the relief of pain, but it is well for a young person with sensitive skin to test the temperature of the water. Hot water bags, especially of the chemical type, are looked on with disfavor. Meticulous care and cleanliness are essential in trimming toe-nails, calluses or corns. In many cases this is better left to a skilled chiropodist who understands the diabetic and vascular conditions. One homely remedy, occasionally effective for patients with low blood pressure and impaired circulation in the legs, is a glass of water at bedtime. Sometimes it permits a night of uninterrupted sleep.

4. NEURITIC TYPE

In this group belong the cases ordinarily described as cases of diabetic neuritis or diabetic tabes. I have observations on 120 such cases to present. Some probably would not be classified as cases of neuritis by many physicians, but they have some features in common and they serve as examples for purposes of discussion. In many cases the same features were present as those exhibited in cases in the three preceding groups, but this is not surprising when one considers the two apparent causes (hyperglycemia and arteriosclerosis) operating in the former groups. Certain other manifestations in the group may represent merely an exten-

sion or exaggeration of the processes in the preceding groups, but the clinical picture and the course of the disease suggest that the condition in these cases is possibly different; and I have put them in a separate group for study, so that conclusions drawn may not be false owing to improper selection. In this group are cases of neuritis possibly resulting from causes other than diabetes and its related concomitants, but I believe that even in these the presence of the diabetes had an effect on the type or degree of neuritis produced. In general, the condition in cases of the neuritic type differed from that in cases of the degenerative type in that the neuritis was usually a cause of real difficulty, the onset was often acute and the neuritis tended to improve markedly within a reasonably short time. In some cases the patient improved rapidly and was free from both symptoms and signs. This contrasts sharply with the chronic course and absence of complete cure in the former group.

Incidence.—It is difficult to determine the incidence of diabetic neuritis because it is difficult to decide what constitutes neuritis. Furthermore, contact with the patient must be maintained from the onset of the diabetes until death, because the neuritis, unlike the diabetes, is at times transient. One author reported the incidence of pain, another the absence of knee jerks and another the frequency of abnormal knee jerks, and another made a more general statement as to the frequency or rarity of the condition.

Bouchard (1884) noted absence of the patellar reflexes in 28.5 per cent of diabetic patients, Auerbach (1887) in from 35 to 40 per cent, Maschka (1885) in 30.6 per cent, Eichhorst (1892) in 18.8 per cent, Grube (1893) in 7.6 per cent, Williamson (1924) in 49 per cent and Melander (1931) in 3.8 per cent. Auché (1890) believed that diabetic neuritis was not a rare complication in diabetes. Pitres (1902) reported 1 case of diabetes in which there was absence of the pupillary reflex and 20 of 32 showing weakness or absence of the patellar reflexes. Williamson (1905) reported decreased vibratory sensitivity in 15 of 45 diabetic patients. Kraus (1922) noted abnormal knee jerks in 40 per cent of 450 such patients. Stewart (1925) stated that the nervous system is involved in 50 per cent of diabetic persons. Von Noorden and Isaac (1927) stated that 31 per cent of diabetic patients have pain, but Woltman and Wilder (1929) noted pain in only 10 per cent and paresthesia not accounted for by arthritis, myositis or trauma in 10 per cent. Wendt and Peck (1931) mentioned persistent pain in 5 per cent of their cases. Murphy and Moxon (1931) reported neuritis in 0.6 per cent of their cases. Sevringhaus (1931) noted pain in 49 per cent and reduced reflexes in 57.3 per cent of his diabetic patients especially examined for these conditions.

This high incidence of neurologic derangement in 1931 seems to cast doubt on the assertion of Melander that the administration of insulin

has decreased the incidence of abnormality of the reflexes by enabling persons with diabetes to remain in better general condition, although he did use absence of the reflexes rather than mere abnormality of the reflexes as his guide. The incidence of diabetic neuritis in my cases was arrived at in two rather inadequate ways. Sluggishness or absence of one or more of the knee jerks or ankle jerks probably gives a fair idea of the presence of the degenerative changes of the nerves, but it includes such an abnormality due to any cause. It indicates the presence of the neuropathy only at the time of the examination and fails to include those cases in which such a neuropathy develops later. Among 461 unselected cases of diabetes, normal knee jerks and ankle jerks were noted in 252 (54.7 per cent), except that the left knee jerk in 1 case was hyperactive. In all other cases there was a decrease of one or more of the four tendon reflexes. In no case was there hyperactivity of the tendon jerks as a whole; in only 2 cases were there hyperactive knee jerks, and in both cases there was absence of the ankle jerks. The knee jerks improved in six months in 1 case, and in another the ankle jerks improved in seven months. There was absence of all the knee jerks and ankle jerks in only 22 cases (4.8 per cent). The second method of determining the incidence of neuritis has its faults also. This study extended over a period of two and one-half years. I noted real neuritis in 25 of 1,000 consecutive cases observed for the first time in the period of this study. Neuritis may appear later in many more of the 1,000 cases, but so far the incidence has been only 2.5 per cent.

Site.—I had 120 patients, 1 of whom had two apparently unrelated attacks of neuritis. The site of the neuritis in these 121 cases was as follows:

	Cases	Percentage
Legs	81	66.9
Arms	8	6.7
General involvement and other special sites	32	26.4

The neuropathy may involve almost any part of the body from the pupils to the feet. The optic, the oculomotor, the facial, the auditory and the recurrent laryngeal nerves have all been affected directly or indirectly, as evidenced by abnormal function of the structure innervated. I have mentioned 1 case in which the condition simulated ureteral colic. Disturbance in the bladder, as revealed by incontinence or by retention with paralysis of the wall of the bladder, has been observed. Cases of abdominal symptoms have been observed. The predominance of involvement of the legs is striking and is in accord with previous reports.

Clinical Picture.—The student of diabetes is apt to forget the ordinary significance of certain neurologic signs. He sees them so often in diabetic patients that he becomes accustomed to changes that would greatly perturb the student of other diseases, who knows these signs are often

of serious portent in nondiabetic persons. To describe the clinical picture of diabetic neuritis, it is necessary to report several cases at least briefly. Others will be described because it is a moot point whether or not the condition was neuritic, and I wish to present them for consideration and discussion. To mention all the symptoms and signs met with in this condition would confuse rather than clarify any ideas of the disease, for they are protean and may simulate many other diseases of the nervous system. It is well to remember that pain (especially at night), paresthesia, decreased activity of reflexes and paresis are the most frequently encountered features and that in the great majority of cases the legs are affected. Even considering the defectiveness of ordinary observation, memory and subsequent description, one is impressed by the vagueness of the condition. It seldom involves only the area innervated by one nerve, and often it does not involve all this small area. Feiling (1921) and Hyslop and Kraus (1923) implied that multiple neuritis and lead neuritis may also be diffuse and cause changes in the central as well as in the peripheral nervous system. The person with diabetes who can definitely outline the boundaries of the area affected by the neuritis is rarely seen. Even the time of onset is not always well marked, although some patients describe a definite, acute onset of symptoms. The very vagueness of the descriptions and the widespread area affected by symptoms or signs suggest a diffuse and patchy involvement of the nervous system, an insidious process rather than an isolated and sharply demarcated one. It is difficult to conceive of true neuritis, involving all the fibers of a nerve trunk, causing most of these neuropathies. It is not unusual to note an abnormal tendon reflex in one leg whereas the patient complained of neuritis of the other leg. Another patient may complain of discomfort in only one leg and yet on close questioning acknowledge symptoms in the other also. The indefinite nature of the condition may be explicable on the basis of two conditions, neuritic and degenerative, affecting the nervous system simultaneously. It is hardly fair to interpret all the changes as being due either to the more acute process or to the chronic degenerative one. It seems definite that at times there is acute neuritis superimposed on a chronic condition. The former responds well to treatment, yet slight symptoms or signs remain, and I am inclined to think that these are due to the chronic condition and are dependent on a different cause from that of the neuritis itself. For example, in case 9,468 there was acute neuritis with foot drop which disappeared within six months. Yet two years later the patient still showed change in the reflexes. I interpret the foot drop and the change in the reflexes as separate conditions. The patient certainly views the two conditions differently. He says that he had neuritis but that now he is cured, and I am inclined to agree, although I believe that now he has a diabetic neuropathy, though of a somewhat different nature.

CASE 1,930.—A woman of 35 years began to have pain and paresthesia. The pain was very severe and shooting and was felt over the entire body. The paresthesia was described as numbness of the toes, as if there were cotton under them. Two months after the onset the patient consulted me and was given the usual diabetic treatment for patients who are not admitted to the hospital. Diabetes was so severe as to be controlled with great difficulty, but the patient stated that there had not been much glycosuria until the neuritis made the diabetic condition worse. Six months after the onset the neuritis was so severe that the patient was admitted to the hospital; but it was another three months before improvement became definite. A year after the patient was admitted to the hospital the neuritis was much better, although another year elapsed before the patient considered herself cured. Three and a half years after the onset of the neuritis, physical examination revealed a sluggish right knee jerk, absence of ankle jerks, soreness of the calves and hypesthesia of the lower part of the legs. At this time the patient was 39 years old, had moderate arteriosclerosis and had had diabetes for more than eleven years. The treatment in this case consisted of treatment of the diabetes, rest, application of heat, removal of abscessed teeth and the addition of liver extract and yeast to the diet.

CASE 3,869.—A woman, 59 years old, with moderate arteriosclerosis and diabetes of three years' duration, had neuritis, which began suddenly with severe pain in the left hip, the posterior portion of the thigh and the lower part of the leg, even to the toes. This was associated with cramps in the calves and numbness in the legs. After six weeks, weakness of the legs developed and caused almost complete paralysis. The knee jerks were normal. Gradually, with the routine treatment for diabetes and neuritis, she improved considerably. At the second visit, seven years later, the patient was still troubled with some paresthesia, cramps and weakness of the legs, especially when there was glycosuria. Examination at this time revealed sluggish knee jerks (especially on the right), absence of the left ankle jerk, weakness of the left peroneal nerve and some weakness and atrophy of the left calf and thigh. The circulation was somewhat deficient in the feet, especially in the left foot. The cholesterol content of the blood was normal. In spite of some discomfort and disability the patient had worked well in the past six years. On the third visit, ten months after the second, examination did not reveal particular change, except that the left ankle jerk was elicited at times. The cholesterol content was 250 mg. The neuritic symptoms appeared occasionally, but the application of heat usually gave relief.

In this case there was an acute onset, and the neuritis responded fairly well to treatment at first, but the symptoms and signs persisted to some extent for more than seven years. It is difficult to believe that the patient suffered from neuropathic involvement from two sources, yet the acute onset and severity of the disability, with improvement at first, are in contrast to the relatively mild symptoms and the prolonged course of the condition in the subsequent period.

CASE 4,319.—A man, 70 years old, with advanced arteriosclerosis and diabetes of eight years' duration, had a left foot drop, with paresthesia. Two months later he consulted me, but because he felt so well he did not follow the treatment prescribed, even though there was considerable glycosuria. The paresis improved, but severe pain developed in the leg six months after I saw him. The pain occurred only at night and never when the patient was walking. One year after the onset of the paresis the patient returned on account of severe pain and a moderate degree of nervousness and depression. There were sluggishness of the right knee jerk, absence of the left knee jerk and of both ankle jerks, weakness

of the entire left leg except the calf, tenderness of the muscles of the leg and hyperesthesia from the hip and groin to the lower part of the leg, at which level deficient circulation became evident. Seventeen days of treatment in the hospital afforded considerable relief.

CASE 5,390.—A man 35 years old, with slight arteriosclerosis and diabetes of five years' duration, was admitted to the hospital with marked glycosuria, which responded well to treatment with diet and insulin. There were no symptoms or signs of neuritis. Abscessed teeth were removed at this time. A few days after the patient became aglycosuric a constant aching developed in his legs, associated with hyperesthesia so severe that even bedcovers caused pain. Numbness and burning of the feet occurred. Seven weeks after the onset of symptoms the patient returned to the hospital on account of the neuritis. Examination revealed absence of the ankle jerks, which had been normal at the time of the first examination. Hyperesthesia was present over the entire body, except on the lateral side of the right thigh. The muscles and nerves from the hips to the feet were tender. In another month he was unable to walk, and he was then admitted to another hospital, from whence he wrote that he was burned while receiving heat treatment, indicating either a change from the previous hyperesthesia to hypo-esthesia or an abnormal susceptibility to heat. While at the other hospital a tonsil became infected. Subsequent to this the patient began to improve, and he was well within ten months of the onset of the neuritis.

CASE 10,925.—A 64 year old man with diabetes of seventeen years' duration had neuritis, with pain in the left leg, tingling in the feet and hyperesthesia. The hyperesthesia diminished gradually, but weakness developed. Seven months after the onset the right leg became involved. There were tenderness of the calves and thighs and weakness of the thigh and iliopsoas muscles, especially on the left side. Sensitivity to pinprick was diminished on the anterolateral portion of the thighs, varying in intensity elsewhere. There was absence of the tendon reflexes in the legs. There were moderate psychic instability and depression, obviously exaggerated by the death of his wife, which occurred during the course of the neuritis. Gradually, during the next five months the neuritis improved markedly, especially in the left leg, which became almost normal.

CASE 10,972.—A 65 year old woman sought treatment because of neuritis, and it was discovered that she had diabetes. The neuritis began as pain in the thigh and then extended to the foot, being present only at night. Weakness of the thigh was noted when the patient went up or down steps. Examination revealed tenderness only of the internal lower aspect of the right knee. There was absence of the right knee jerk, but the other three tendon jerks in the legs were normal. There were atrophy of the right quadriceps muscle and weakness of the quadriceps and iliopsoas muscle on the right. The neuritis improved within a month after the onset, but a relapse occurred, the pain and tenderness returned, and the weakness of the leg increased so that the patient could not raise the leg to a couch nor could she rise from a sitting position. Psychic depression became marked. In another month the patient was much better and walked 1½ miles (2.4 Km.) daily. Six months after the onset she considered herself well, and the depression had disappeared.

CASE 8,428.—A 30 year old man with diabetes of one and two-tenths years' duration began to have slight numbness of the lower portion of the right leg. After about two and one-half weeks this became more noticeable but was still rather negligible. Three days later, as the patient was walking home, slight pain began in the leg and increased in about thirty minutes to such severity that he

called a physician, who recommended the application of an electric pad. Under the soothing effect of the heat, the patient fell asleep, to awake five hours later to find his foot badly burned. Within three days the pain decreased markedly, but he consulted me because of the burn. Examination revealed a queer burn on the lateral surface of the right foot and on the tips of the toes. The skin was dry, hard and discolored, like dry gangrene. There was a slight formation of blisters in spots. The foot was dry and cold, and the pulse was not detectable below the femoral artery; but the other foot seemed just as cold and had a palpable dorsalis pedis pulse. There was slight arteriosclerosis. There was absence of the right ankle jerk, and there was cutaneous anesthesia roughly in the area supplied by the external popliteal nerve but also of the whole foot except a small part of the dorsum. There was absence of position sense of the right great toe. There was tenderness of the external popliteal nerve.

The patient was admitted to the hospital, where readings for temperature of the skin showed lower values for the left than for the right foot, although the latter was colder than normal. The right foot was dry and the left was moist; and by wetting the right foot with a damp cloth I noted that the resulting evaporation lowered the temperature of the skin to the level in the other foot. I concluded that the sympathetic fibers to the right foot were damaged and that possibly a reflex stimulation of similar fibers to the other foot had caused the excessive sweating and lowering of the temperature in spite of uninterrupted circulation through the arteries. Owing to the inactivity resulting from the surgical treatment, foot drop developed on the right side, even though the ankle jerk and position sense had been partially regained; but eleven days of passive and active exercise overcame the foot drop. Gradually sensation returned in the previously anesthetic area. One may regard the whole attack as being due to sudden occlusion of the artery; but why such a sudden onset without demarcation, why the decrease of pain and return of the ankle jerk and position sense within a few days? Why, if the femoral or popliteal artery was occluded, was only the peroneal nerve affected? It seems more likely that neuritis developed in a limb to which the artery had been occluded slowly (about fourteen months previously the dorsalis pedis pulse was present) and that this vascular change played the rôle in the development of the neuritis that arteriosclerosis usually plays in older patients.

Symptoms.—Pain was present in 83.3 per cent of the cases. The most prominent characteristic was intensification at night and relief when the patient walked. The pain was at times dull, at other times sharp, sometimes continuous and sometimes shooting and momentary. Occasionally the pain was cramplike, burning, crushing or grinding. Usually it was ill defined, but occasionally it was limited to the course of one nerve, such as the sciatic. Of the 20 cases in which there was no pain, there was muscular paresis in 16, paresthesia in 2, optic neuritis in 1 and absence of reflexes in 1, with return of one knee jerk almost to normal in one year. Although frequently causing pain and other symptoms on the anterolateral surface of the thigh, diabetic neuritis differs distinctly from meralgia peraesthetica (Huddleson, 1928) in that the pain of the former is usually worse when the patient is in bed and is often relieved when the patient paces the floor. Paresthesia occurred in 70 per cent of all the cases and was often worse at night. The

paresthesia assumed the form of numbness, tingling, prickling, burning, coldness and a sensation as if the patient were walking on wool. Dizziness was occasionally experienced. Certain special symptoms will be described more fully later.

Signs.—Tendon Jerks: The most frequent sign was hyporeflexia, or areflexia, which occurred in 75.4 per cent of the cases. Sometimes, as in cases 8,167 and 10,279, the change in reflexes was more marked in the leg less affected otherwise by the neuritis. In general, when a change in the reflexes occurred, it was present in the area otherwise affected by the neuritis; but sometimes there was no change, and in many cases the changes occurred in areas otherwise free from neuritis.

Paresis: Muscular paresis, varying from slight weakness to complete paralysis (case 11,044), occurred in 65.8 per cent of the 111 cases in which a record of this sign was made. In each of 30 cases various muscles of the leg were affected. In 31 cases the dorsiflexor muscles of the foot were involved (bilaterally in 1 case), and in 16 of these no other muscles were weak. The quadriceps femoris muscle was involved in 21 cases, in 7 of which there was no other weakness. The hamstring muscles were affected alone in 2 cases and in conjunction with other muscles in 6 cases and the iliopsoas muscle alone in 2 cases and with other muscles in 8. In 3 cases there was weakness of some group of muscles of the arm. In 1 case (case 9,230) there were weakness and atrophy of both arms and legs. The paresis is not detected with ease in all cases. A patient lying in bed may not notice foot drop, and repeated examinations of bedridden patients are advisable, in order that paresis may be discovered promptly and corrected before it has become severe. Some patients suffered falls; some had difficulty in stepping up into a street car or in climbing or descending steps, and some recognized the difficulty by the flapping of the foot when they walked. In case 9,360 syphilis was suspected because of the unsteady and steppage gait, which Charcot (1890) described. At times the paresis is sufficient to incapacitate the patient completely. Atrophy may or may not be present. Occasionally it is marked and at other times slight; sometimes it is well localized and at other times widespread and manifested merely by the smaller circumference of the affected leg. As in case 4,319, paresis may be the initial symptom of the neuritis, and pain may not supervene until several months later.

Atrophy of Muscles vs. Atrophy Caused by Injection of Insulin: In connection with atrophy of muscles one might consider briefly the atrophy caused by the injection of insulin sometimes observed in persons with diabetes. No connection between this form of atrophy and diabetic neuropathy has been observed. In 1 patient (case 9,832) who had been injecting insulin in the arms and legs for about six years, I noted numerous areas of atrophy, some at sites where the patient said she had not

injected insulin, although the atrophy was in the general vicinity of the injections. The areas of atrophy were said to have appeared regularly overnight in the limb in which the injection was made the preceding day, and the many areas appeared in the course of one month. Furthermore, the husband said that the areas of atrophy appeared only when the skin was prepared with alcohol, never when mercurochrome or iodine was used. Examination revealed obvious atrophy of the subcutaneous fat, and it did not follow the course of a cutaneous nerve. There were no tenderness or abnormal sensation at the site, no muscle weakness and no abnormality of the reflexes. If atrophy occurred through the medium of nerves, it must have involved only the tiny peripheral branches. The occurrence of all the changes in only one month of the six years during which insulin had been used suggests that possibly a particular supply of insulin was at fault.

Tenderness.—Tenderness other than hyperesthesia of the skin was noted in 61.2 per cent of the 98 cases in which the condition was recorded. One may contend that neuritis without tenderness does not occur. I do not insist that this is a form of neuritis involving all the fibers of one nerve trunk. I believe it more likely that it is a patchy involvement which is not limited to the peripheral nervous system. In 35.6 per cent of the cases of muscular paresis, which is good evidence of a real neurologic disturbance, no tenderness was present. In other cases, as in the 2 with involvement of the optic nerve, the affected nerve cannot be examined for tenderness or else it does not carry such sensory fibers. Even when tenderness exists, it usually is not limited to the nerve itself but often is just as marked in the muscles.

Sensation to Pinprick and Touch: For cutaneous sensitivity the patients were tested only by pinprick and by light touch of the hand. I used the test for sensitivity to heat and cold only occasionally and observed that it yielded results similar to those obtained with the test for pain. Cutaneous sensitivity was tested in 100 of these cases and was found to be abnormal in 51. Hypesthesia was noted in 56.9 per cent of the 51 cases, hyperesthesia in 29.4 per cent and a combination of the two in 13.7 per cent. The area affected is seldom sharply demarcated, and areas of normal sensitivity are interspersed between abnormal areas. In general hypesthesia involving the lower part of the legs is more marked in the lower portion and gradually changes to normal sensitivity at about the level of the knee. I have attributed this in many cases to impaired circulation at the lower level; but often diabetic persons with infections or trophic lesions of the feet and relatively good circulation have greater insensitivity than those with gangrene and poor circulation. This lends some support to the conception that these lesions are at least partially neurogenic, as was suggested by Buzzard (1890) and Lépine (1909). The case reported by Holt (1928) was of this type. However,

there are cases with associated gangrene in which no pain is experienced during surgical maneuvers (case 10,582), and rarely one sees a diabetic patient with circulation so poor that amputation is carried out, and yet surgical procedure causes severe pain (case 9,429). McKittrick and Root (1929) attributed the trophic ulcers of the feet to pressure, poor circulation and infection rather than to a neurologic cause; but blisters and ulcers on the feet occur at times without an obvious precipitating cause. Some patients (cases 5,361 and 5,390) have had hyperesthesia and also sufficient hypesthesia to burn themselves without noticing the pain. Two other patients (cases 2,411 and 8,428), suffering only from hypesthesia, burned themselves and felt absolutely no pain.

Position Sense and Ataxia: Considering the lesions in the posterior columns described by many authors, one would expect to find ataxia and loss of position sense frequently, but this has not been true in my experience. I tested for position sense in 82 cases and noted that there was decrease or absence in 13 (15.9 per cent). In 4 of these 13 there was a history of at least a slight consumption of alcohol, and in 1, of syphilis. One patient had pernicious anemia, 1 had secondary anemia and 1 had ocular lesions attributed by the ophthalmologist to syphilis, but there was no other evidence of syphilis according to the history, physical examination or serologic study. There remained 5 cases in which there was no evidence of alcoholism, syphilis or anemia in which there was loss or decrease of the position sense. Ataxia was very rare; in this series it was recorded only four times, for 1 patient with syphilis, for 1 with combined system disease and for 2 who said that they consumed small quantities of alcohol. In the following case the patient was definitely addicted to the use of alcohol as well as being diabetic.

CASE 5,841.—A 55 year old man began to have severe shooting pains throughout the whole body, especially in the legs and especially at night. Burning sensations supervened. Finally, the patient noticed that he had to watch his feet when he walked. The examination revealed tenderness of the nerves, hyperesthesia of the legs with an indefinite upper level, slight weakness of the flexor muscles of the feet and slight general weakness, slight ataxia and sluggish tendon jerks. Galvanism made the symptoms worse. In eighteen months, with diabetic and general treatment, the patient was able to walk normally, and he seemed to be cured of the neuritis.

Fever.—An elevation of temperature was recorded in 25 per cent of the 112 cases in which readings of temperature were made. The elevation was usually slight, and the temperature was never high, ranging from 98.8 to 100.6 F. In some cases there were days of normal temperature interspersed between days with fever. Many patients other than the 28 mentioned here had fever due to some obvious cause, but in these 28 cases no cause was found, unless it was the diabetic neuropathy.

Leukocytosis and Differential Count.—Of the 50 patients for whom a white blood cell count was carried out, 13 (26 per cent) had more than 10,000 white blood cells, and 4 of these also had fever. Ten of the 13 patients had a normal blood smear, examination of the blood smear was not carried out for 2, and for 1 the cell count showed 85 per cent polymorphonuclears. Of the 4 patients with fever and leukocytosis, only 1 had an abnormal blood smear (85 per cent polymorphonuclears). In 47 cases a study of the blood smear was made. Three of the patients had pernicious anemia, and 32 others were normal. For the remaining 12 the cell count was as follows: 3 had 6 per cent eosinophilia, 3 had 3 per cent eosinophilia, and the other 6 had, respectively, 66 per cent lymphocytes, 56 per cent lymphocytes, 42 per cent lymphocytes, 85 per cent polymorphonuclears, 56 per cent polymorphonuclears and 49 per cent polymorphonuclears. I have no explanation for the slight eosinophilia. Foci of infection and obvious anaphylaxis were not present. One patient was taking liver extract, but the others were not. Of the 113 patients examined for fever or leukocytosis, 25.7 per cent had a temperature of at least 99 F. or a leukocyte count of more than 10,000 cells.

Spinal Fluid.—The spinal fluid was examined in 40 cases included in this study. In 3 of these the spinal fluid was normal. In 3 others an abnormality was not recorded, but no mention was made of the protein content. One patient was definitely syphilitic, and the values will not be considered except for the sugar content. The total protein content varied from 35 to 120 mg. per hundred cubic centimeters, being above 50 mg. in 22 cases and above 60 mg. in 15 cases. Globulin was noted in the fluid in 33 cases, there being more than a slightest possible trace in 18 cases. One specimen was bloody and contained 286 white cells. In 1 other specimen there were 9 white cells. In all other specimens the white cell content was well within the normal limit. The colloidal gold curve was normal in all cases in which it was recorded, except that in case 10,451, that of the patient with the Charcot joints, it was 3444310000 and in case 8,428 it was 0123210000. The spinal fluid and blood were obtained simultaneously in 22 cases. The sugar content of the spinal fluid varied from 80 to 150 mg. per hundred cubic centimeters, with an average of 99.5 mg., and its ratio to the sugar content of the blood varied from 34.8 to 85.7 per cent, with an average of 54.5 per cent. Rieger and Solomon (1916) reported the sugar content of the spinal fluid of 175 persons. They observed a range from 50 to 90 mg., with an average of 70 mg., except for the extremes noted in persons with diabetes and inflammatory conditions. Six diabetic persons yielded values ranging from 134 to 256 mg., but that was in the era before the use of insulin. Wahl (1931) reported simultaneous values of the blood and spinal fluid sugar for 5 patients. The ratio of

sugar in the spinal fluid to that in the blood was 75 per cent, being higher in the uncontrolled cases; and Steinitz' (1931) results were rather similar. My results show that the ratio for those patients with a sugar content of the blood of 200 mg. or more was less than the average for the whole group. The spinal fluid in the cases reported on by Major (1924), Angle (1928) and Root and Rogers (1930) contained more than the normal amount of protein. Furthermore, in Angle's case there were 30 cells per cubic millimeter. In the case of diabetic tabes reported by Bostock (1926) there were also many cells and other abnormal findings in the spinal fluid, but the patient may also have had syphilis. In the case reported by Wright (1931) there were an increased gobulin content and a colloidal gold curve of 1123210000.

Special Features.—Pupillary Changes: Pupillary changes (including Argyll Robertson pupils) not due to syphilis have been reported in various conditions,[8] including neuritis and arteriosclerosis. Moore (1931) reported cases in which no known cause was noted. That diabetes is a cause of Argyll Robertson pupils was denied by Williamson (1907), Smith (1926) and Grafe (1927) but affirmed by Parker (1928). Adie (1931) and Merritt and Moore (1933) insisted that the true Argyll Robertson pupil is found only in syphilitic persons, and that those attributed to other conditions do not fulfil the requirements of Argyll Robertson. Pryce (1887) and Major (1924) each reported the case of a diabetic person with sluggish pupils, and Pitres (1902) noted the absence of the pupillary reflex in 1 of 32 diabetic persons. Laudenheimer (1896) reported the case of a diabetic patient with unequal pupils, and Ingegnieros (1905) mentioned the case of a diabetic patient with poorly defined Argyll Robertson pupils. I have encountered changes in the pupillary reflex in many diabetic patients for which there was no explanation except the diabetes. Most of my 23 patients with pupillary changes had definite abnormalities, although 1 patient had only inequality and irregularity of the pupils and 2 others had unequal pupils which reacted normally according to one observer but not according to another. In the other 20 cases there were indisputably abnormal reactions to light and distance or to light alone. A true Argyll Robertson pupil (fixed to light, reacting to distance, dilating only partially with mydriatics and in some cases contracted) was noted in 5 cases, and in 8 others there was sluggish response to light, with a normal response to distance. In 7 cases the pupils were fixed or sluggish to both light and distance. Irregular pupils were observed in 7 cases and unequal pupils in 5. Syphilis was not present in these

8. Tinel and Goldflam (1912). Mériel (1926). Thomas (1931). Wilson and Robertson (1932). Nielsen and Verity (1930). Feiling and Viner (1922). Ashby (1927). Voegtlin and Lake (1919). Woltman (1921). Price (1923).

cases according to the history, physical examination and Wassermann reaction of the blood. In 5 cases spinal puncture was carried out, and the spinal fluid did not show evidence of syphilis. In all the cases, of course, diabetes was proved, and in all but 1 there were other neurologic changes usually attributed to diabetes. One case was of the circulatory type, 13 of the degenerative and 8 of the neuritic. One was in the group with changes in the bladder. The youngest patient was 37 years old, but he was an astonishingly heavy drinker of whisky. The other 22 patients were 49 years of age or more, and all 23 had arteriosclerosis, in only 2 of whom it was of slight degree. In résumé, in 20 of these 23 cases there were definite abnormalities of the reflexes, with no apparent cause other than diabetes, arteriosclerosis and, in 1 case, alcoholism, although in 6 other cases the patient admitted some consumption of alcohol in the past.

Involvement of the Optic Nerve: Involvement of the optic nerve or retrobulbar neuritis has been described in connection with various conditions,[9] including peripheral neuritis. It has been mentioned in association with diabetes,[10] but other authors [11] have questioned or ignored this relationship. I have examined 2 diabetic patients with neuritis of the optic nerve with no obvious cause unless it was diabetes. One patient (case 9,312) with diabetes and arteriosclerosis had diabetic neuritis of the legs, which was quickly relieved. She then had some abscessed teeth removed. Several weeks later neuritis of the optic nerve developed. A boy (case 3,880) of 13 years had neuritis of the optic nerve without any apparent cause except the diabetes. In both these cases recovery occurred with no treatment other than the usual diabetic regimen.

Paresis of the External Ocular Muscles: Paralysis of the ocular muscles in persons with diabetes, according to Collier (1930), was described first by Ogle (1866). Lyon (1891) and Dieulafoy (1905) noted the frequency of this association, as did Collier, although Parker (1925) believed otherwise. Such paralysis may not always be apoplectic, as Collier stated. At times it resembles paralysis of the muscles of the legs associated with diabetes. The onset is not always abrupt, and recovery is rapid and complete in some cases. Furthermore, the

9. Mayou (1926). Davis (1923, 1926). Harris (1914). Archer-Hall (1920, 1922). Smith (1929). White (1916). Stark (1921). Crane (1927). Mason (1922). Mahoney (1932). Aub.

10. Tardieu (1862). Moore (1862). Raven (1887). Fraser and Bruce (1895, 1896). Moore (1921). Cohen (1923). Francis and Koenig (1926). Wagener (1929). Grafe (1927). Collier (1930). Dunphy (1930). Manes and Malbran (1931). O'Donoghue (1931).

11. Lépine (1909). Smith (1926). Parker (1925). Davis (1926). Paterson (1927).

condition of the eye is frequently associated with signs of diabetic neuropathy in other parts of the body, occurring in 3 of the 5 cases reported by Root (1922). Defective cranial nerves have been reported in other forms of neuritis,[12] and I have noted changes in the pupillary reflexes apparently due to diabetes. I report 1 case of diabetes with paralysis of the ocular muscles.

CASE 10,045.—A 64 year old man with diabetes of seven and eight-tenths years' duration had paralysis of the muscles of the eye which developed over a period of from one to three days. Examination revealed moderate arteriosclerosis and paralysis of both superior rectus muscles and of the left external rectus muscle.

The involvement of the various muscles of the eye is difficult to explain on the basis of hemorrhage or thrombosis, and the onset of the condition was not abrupt. Furthermore, the patient had had pains in the legs, and the biceps reflexes were sluggish, although all the other reflexes were normal.

I report these cases only that they may be given consideration and not with the intention of classifying cases of this type in a definite way. The course in some of them resembles so much that in cases of diabetic neuritis and the association of arteriosclerosis and such neuritis occurs so often that I wonder if perhaps at times the ocular paralysis may not be of a nature similar to that of the neuritis.

Involvement of the Auditory Nerve: Neuritis of the eighth cranial nerve has been described. Davis (1916) reported the condition in syphilitic patients; MacKenzie (1916) reported it in a case of unknown origin, and Young (1932) reported the case of a patient with a polyneuritis with progressive tinnitus and nerve deafness. Wittmaack (1907), Heiman (1907) and Merrill (1911) described involvement of the eighth nerve in persons with diabetes, Merrill attributing it in his case to the toxemia of diabetes. I observed 1 patient (case 10,262) in whom deafness developed during the course of diabetic neuritis and whose hearing improved as the neuritis improved.

Facial Paralysis: Whether or not facial paralysis is ever of the nature of diabetic neuritis is difficult to say. That it is at times of an apoplectic nature is certain, but in the cases of peripheral origin it is not easy to say that it is not of the type seen in nondiabetic patients. Grégoire (1883) and Bernhardt (1899) noted the frequency of facial paralysis in diabetic patients, the former (according to Auché [1890]) attributing it to bulbar lesions. As mentioned before, facial paralysis occurs regularly in one type of polyneuritis, and it is not impossible that the condition occurring in diabetic patients is of the nature of diabetic neuritis. I included 2 cases of diabetes with facial paralysis

12. Grimberg (1928). Taylor and McDonald (1932). Wilson and Robertson (1932). Déjérine (1914). Buzzard (1890). Aub.

in this series. In 1 (case 6,776) there was no other neuritic change. In the second (case 5,361) painful diabetic neuritis developed, involving both legs, which was still present the last time I saw the patient. In each case recovery of the facial movements was almost complete in about one year.

Paralysis of the Vocal Cord: I had 1 patient (case 9,429) who suffered from temporary paralysis of the superior laryngeal nerve associated with some tenderness of the thyroid region. New and Childrey (1930) reported paralysis of this nerve associated with arteriosclerosis of the central nervous system, and my patient had moderate arteriosclerosis and signs of degenerative neuropathy of the legs. The neuritis in this case may have been the result of thyroiditis of unknown origin and may have had no connection with the diabetes.

Abdominal Symptoms: The resemblance between tabes and diabetic neuritis has been commented on often, but usually with the reservation that Argyll Robertson pupils, Charcot joints, gastric crises and disturbances in the bladder do not result from diabetes. I have already described the pupillary changes and the presence of Charcot joints in 1 case, and now I shall discuss the other two conditions.

Case 4,127.—A 65 year old woman with diabetes of seven and nine-tenths years' duration was admitted to the hospital on account of nausea and abdominal pain. The symptoms, of four days' duration, were severe but occurred only at night and were relieved by walking. The examination revealed nothing abnormal except arteriosclerosis and diabetes. Roentgen examination disclosed no abnormality. A thorough search for diaphragmatic hernia gave negative results. After a week at the hospital, with symptomatic and diabetic treatment, the nausea stopped, and the pain diminished considerably. In this case the nocturnal occurrence of symptoms relieved by walking and recovery with the usual diabetic and symptomatic treatment suggested the possibility of diabetic neuritis.

Case 10,559.—A 63 year old woman was admitted to the hospital with uncontrolled diabetes and pain in the leg associated with sluggish knee jerks and absence of ankle jerks. Regulation of the diabetes relieved the pain at once. Four months later the patient was readmitted with more definite neuritis in the leg. This improved with treatment but recurred and persisted and became more widespread. Four months after the second visit she was admitted again. During the three months prior to admission, in addition to the obvious neuritis, the patient had had abdominal symptoms, beginning as a band of pain on the left side of the lower portion of the chest and the upper portion of the abdomen and after three weeks involving the right side also. The pain was always worse at night. After two months, the patient began to vomit, and this continued to the time she was admitted to the hospital. As a result of the pain, vomiting and small intake of food, the patient was very thin, weak and a "nervous wreck." Her neurosis was exceptionally severe, but it was interspersed with occasional days of dilapidated cheerfulness. Roentgen examination did not reveal pathologic changes except a gallstone. With symptomatic treatment the patient improved somewhat, but progress was so slow that operation for the gallstone was performed. The stone was reposing in an otherwise normal gallbladder, and no other abdominal abnor-

mality was disclosed. The vomiting, which had subsided just before the operation, recurred, and there was no amelioration of symptoms other than would be expected from the supportive treatment. The psychic disturbance was so great that the family acceded to the patient's request to take her home. During the next six months, with diabetic treatment, the nausea and vomiting stopped, and the neuritis in the legs improved.

This patient had definite diabetic neuritis and vague abdominal symptoms of insidious onset, similar to those of the usual neuritis. It is known that neuritis causes paresis of the skeletal muscles and that the psychic state of the patient varies in direct relationship to the neuritic symptoms. This patient had gastric atonia, and the gastric symptoms were better when she was less depressed. When depressed she would vomit almost as soon as the fluid intake by mouth amounted to from 16 to 24 ounces (472 to 708 cc.), but not when she was cheerful.

In 2 more of the cases of neuritis abdominal symptoms were present, the condition in 1 (case 11,113) suggesting carcinoma of the cecum or the ascending colon. The patient may have had carcinoma, but the roentgen and physical examinations gave negative results. Pain was worse at night, and it extended into the leg and was associated with muscular paresis. Pryce (1919) reported a case of neuritis of the leg in which subsequently the condition seemed to be due to a probable carcinoma that was not discovered on the first examination. Time may prove that the condition in my case was similar, but I have been unable to trace the patient, even though her son is a physician. In case 9,009 the condition was tentatively diagnosed as ureteral colic. Pain began in the posterior portion of the left flank and had gradually extended around to the groin and testicle at the time the patient was admitted to the hospital. The pain was excruciating, in spite of injections of morphine. Gradually, the pain extended into the left leg and within a few days had reached the foot, disappearing above as it spread below. The tenderness moved with the pain from the region of the kidney to the leg, and muscular paresis and hyperesthesia of the leg appeared. The knee jerk, at first only sluggish, disappeared completely, to return in three months as the neuritis improved. Roentgen and urologic examinations did not disclose evidence of genito-urinary disease, and the subsequent course of the condition showed that it was definitely neuritis.

Other abdominal symptoms, such as those reported by Fiske (1925) and those occurring in diabetic acidosis, are not considered here.

Disturbances in the Bladder: I am sure that disturbances in the bladder similar to those noted in syphilitic patients do occur in non-syphilitic persons with diabetes. Such changes are observed often in cases of tumor of the spinal cord and combined symptom disease; and such involvement has been reported with alcoholic neuritis by Boxwell (1914) and Campbell (1924), with lead poisoning by Campbell (1924) and Caulk and Greditzer (1916; 1917), with polyneuritis by Holmes (1917), Harris (1923) and Campbell (1924) and with diphtheritic neu-

ritis by Kennedy (1933). Thus, it is hardly surprising that one occasionally sees such a condition in diabetic patients. Le Bret (1852) was quoted by Marchal de Calvi (1864) as having reported the case of a diabetic person with slight disturbance in the bladder, but he did not disclose the nature of the disturbance. Bonardi (1897) reported the case of a diabetic patient, 72 years old, with loss of sphincter control. Von Noorden and Isaac (1927) referred to urinary urgency, especially at night, not apparently due to the polyuria shown by diabetic persons. McKittrick and Root (1929) reported neurogenic disturbances in the bladder in patients with diabetes. In the case of tabes diabetica reported by Angle (1928) symptoms in the bladder were relieved by the diabetic treatment, but there was also an enlarged prostate, and it seems probable that symptoms in the bladder were due to swelling of an already enlarged prostate, irritated by the uncontrolled diabetes.

I have examined 12 diabetic patients with urinary retention or incontinence or both, apparently due to diabetic neuropathy. None of the patients was syphilitic, nor did I find evidence of any nervous disease except diabetic neuropathy. The symptoms were not dependent directly on uncontrolled diabetes in the ordinary sense of the word or on a basically urologic factor. Seven of the patients had urinary retention, and the other 5 had incontinence suggestive of paresis of the sphincter. The first 7 cases are being reported in the ARCHIVES OF INTERNAL MEDICINE. In 7 cases the symptoms in the bladder began during the course of diabetic neuritis, and in 2 others there were signs indicative of the degenerative diabetic neuropathy. Arteriosclerosis was present in 11 cases and was not mentioned in the twelfth. The youngest patient was 42 years old.

CASE 5,494.—A 47 year old man noted involuntary urination at night at the onset of the diabetes. Five years later he noted paresthesia of the legs and, subsequently, pains in the legs. Two years later the bladder was observed to be distended (residual urine, 360 cc.). Examination revealed: moderate arteriosclerosis; normal pupils and cranial nerves; sluggish knee jerks and ankle jerks; weakness, atrophy and fibrillary twitchings of the muscles of the legs and less of the arms, and variable cutaneous sensitivity, with areas of both hypo-esthesia and hyperesthesia. The Wassermann reaction of the blood was negative, and the spinal fluid was normal, except for the slightest possible trace of globulin. A history of alcoholism was not obtained. Urologic examination revealed slight irregularity of the prostate, which was insufficient to cause obstruction. Trabeculation of the bladder was moderate.

The patient died seven months after examination of gas bacillus infection following an appendectomy.

CASE 9,759.—A 62 year old woman with diabetes of five and one-half years' duration and moderate arteriosclerosis was suffering from progressive diabetic neuritis of rather recent onset. During the evolution of the neuritis, she noted difficulty in retaining the urine. There was no burning or urgency but merely

difficulty in retaining the urine after a certain length of time. Examination did not disclose distention of the bladder or infection of the urinary tract. The knee jerks and ankle jerks, which had been normal a few months previously, became sluggish as the neuritis in the legs progressed. Considerable psychic depression also supervened, such as is often seen in cases of diabetic neuropathy. Although there was achlorhydria, there was no other evidence of combined system disease. There was no history of alcoholism or syphilis.

Although there is something horribly similar between syphilis of the nervous system and diabetic neuritis, there is also something pleasantly different. In the latter condition markedly incapacitating symptoms seldom occur, and this period of incapacity usually passes within a few months. Nor do the changes in diabetes usually progress or persist to the degree seen in syphilis. A diabetic person rarely experiences individually the many infirmities which one not infrequently sees in a tabetic patient.

Psychic Symptoms: The occurrence of psychoses with nonalcoholic neuritis and with plumbism was noted by Korsakow (1890), Harris (1923) and Aub. Cerebral symptoms, probably apoplectic, were described in diabetic patients by Marchal de Calvi (1864) and Desbonnets (1899); and Miles and Root (1922) and Dashiell (1930) studied the mental efficiency of diabetic persons. Depression, hypochondriasis, delirium, suicidal tendency, hallucination and ideas of persecution have been described.[13] Many times these symptoms were not produced by painful neuritis. Alcoholism was present in some cases but not in all. Masson (1923) listed diabetic toxin, arteriosclerosis, menopause and heredity as etiologic factors. The prognosis supposedly varies directly with the control of the diabetes. Diabetic pseudoparesis was mentioned by Laudenheimer (1896), Ingegnieros (1905, Bostock (1926) and Williams (1932). Diabetic treatment proved efficacious in the cases of the first three authors.

The psychic state usually encountered in patients with diabetic neuritis is evidenced by inordinate depression and emotional instability. Nervousness is often extreme, and the patient will neither rest nor be comforted. At times the symptoms are out of proportion to the apparent severity of the neuritis. Of 105 patients with neuritis, 52.4 per cent showed a sufficient degree of depression or nervousness to mark them as abnormal, and 14.3 per cent showed a marked degree of it. One patient (case 9,680) was totally irresponsible and was confined in a psychopathic hospital with a diagnosis of involutional psychosis. She also had neuritis of the external popliteal nerve. Another patient (case

13. Legrand du Saulle (1877, 1884). Lépine (1909). von Liebe (1889). Cohn (1892). Laudenheimer (1896, 1898). Madigan (1883). Mendel (1889). Bond (1896). Halberstadt and Arsimoles (1911). Sittig (1912). Singer and Clark (1917). Pike (1921). Reiter (1926).

6,659) became extremely irritable and completely unmanageable and suffered at home from brainstorms, so that his mother was forced to take him to a sanatorium for safe-keeping, but on the trip his psychic and neuritic symptoms improved so much during a stop at a "hot springs" resort that confinement in the institution became unnecessary. With continued physical therapy, especially massage, the patient recovered completely.

Not only do psychic symptoms occur in persons with neuritis, but neuritis is prone to affect nervous patients with diabetes. About 60 per cent of the first 100 neuritic patients examined had a nervous temperament. This may be due to the susceptibility to injury of a sensitive nervous system or to the more frequent detection of neuritis in complaining than in phlegmatic persons. Twice following emotional shocks one patient (case 9,340) had an exacerbation of symptoms. Such nervousness makes difficult an accurate estimation of cutaneous sensitivity and improvement in the neuritis.

Differentiation Between Poliomyelitis and Neuritis.—Included in this series are 2 cases which puzzled my associates and me because we could not decide whether the condition resulted from the effects of anterior poliomyelitis or from neuritis. To differentiate between these conditions is not always easy, as Dejerine (1914), Joughin (1915) and Harris (1923) pointed out. Involvement of the cells of the anterior horn of the spinal cord has been recorded in various forms of neuritis: in experimental beriberi by Eijkman (1897), in lead poisoning by Hyslop and Kraus (1923) and in diabetes by various authors.[14] In some cases of diabetic neuritis there is rather sudden paralysis of isolated muscles or groups of muscles without other signs of neuritis. The 2 cases included in this study may fall into that group or there may have been true poliomyelitis. I dare say that the condition in both cases would have been unquestionably accepted as neuritis if it had occurred in elderly patients. In the following case the condition was diagnosed as poliomyelitis by the orthopedic consultant and as probable neuritis by the neurologist.

Case 9,230.—A boy of 18 years, with diabetes of five weeks' duration, was unconscious when admitted to a hospital, where he was treated for diabetic coma. When he regained consciousness he complained of pains in various places and weakness of various muscles. Shortly afterward he was transferred to the New England Deaconess Hospital. I observed that all the muscles were weak and small. There was wrist drop, and the triceps muscles were very weak. The muscular paresis involved the legs but to a slightly less extent than the arms. There was absence of the triceps reflexes and of the right knee jerk. The left

14. Leichtentritt (1893). Nonne (1896). Bonardi (1897). Marinesco (1901). Findlay (1902). Bramwell (1907).

knee jerk was sluggish. All other tendon jerks were normal. There was considerable tenderness of both the muscles and the nerves, especially of the upper radial and the right femoral muscle and nerves. The left wrist was swollen, and the patient said that his feet had been swollen just after he recovered from coma. He also stated that his right thumb had been numb, possibly before the onset of coma as well as after. Improvement began in about five weeks and was practically complete in nine months. Fifteen months after the onset the patient had no symptoms and felt as strong as ever; but atrophy, especially of the muscles of the shoulder and the left triceps muscle, was still present, and the left radial tendon jerk and both triceps reflexes were slightly weak.

In 1 other case (case 10,405) the patient first noted paralysis after he recovered from diabetic coma. This patient had merely a left foot drop, which disappeared in six months with the usual treatment for diabetes and neuritis.

Pathology.—We have no pathologic data on these cases. Auché (1890) described myelin degeneration and other changes in the nerves of a young diabetic patient with neuritis, and Wittmaack (1907) described degeneration of the eighth cranial nerve of a diabetic girl 10 years old. It is possible that the pathologic changes in these cases with neuritis were similar to those described by other authors in the cases with associated degenerative neuropathy.

Etiology.—The etiology of the neurologic changes in diabetes has been variously attributed, at least partially, to the excess of sugar,[15] cachexia,[16] venous congestion of the abdominal organs (Rosenstein, 1882), incomplete combustion of the organic acids (Charrin and Guignard, 1882), vascular disease,[17] dehydration (Auché, 1890; Dieulafoy, 1884), an unknown toxin due to the diabetic condition,[18] acetonemia [19] and deficiency disease (Harris, 1922). Auché studied the effect of various solutions of sugar on nerves and concluded that sugar alone was not the cause of these changes, although in concentrated solution it caused injury. Eichhorst (1892) put nerves in solutions of dextrin, acetone, beta-oxybutyric acid and physiologic solution of sodium chloride and did not note distinguishing changes. Pitres and

15. Marchal de Calvi (1864). Christi-Buicli (1873). Worms (1880). Drasche (1882). Barth (1883). Dreyfous (1883). Florain (1885). von Hösslin (1886).

16. Althaus (1890). Raymond and Oulmont (1881). Bernard and Féré (1882). Pryce (1893). Woltman and Wilder (1929).

17. Bouchard (1882). Pryce (1893). Woltman and Wilder (1929). Root and Rogers (1930). Labbé (1931).

18. Fraser and Bruce (1896). Pryce (1887). Eichhorst (1889). Auché (1890). Merrill (1911). Pike (1921). Williamson (1907). Sergent and Kaufmann (1925). Root and Rogers (1930).

19. Auché (1890). von Liebe (1889). Cohn (1892). Laudenheimer (1898). Lépine (1909). Sittig (1912).

Auché (1901) were unable to produce neuritis by the injection of sugar, but Wright (1931) said that Grube reported marked neuritis after such an injection.

In my group of cases with neuritis were some in which neuritis evidently developed, at least partially, from factors not connected directly with the diabetes. I consider these factors as accessory or precipitating causes, because I believe that the diabetes first makes the patient abnormally susceptible to such factors.

Sex and Age: Sixty-nine patients (57.5 per cent) were female and 51 (42.5 per cent) were male. The age at the onset of the neuritis varied from 13 (in case 3,880, with optic neuritis) to 76 years (case 990), the average age being 54.7 years. Only 12.5 per cent of the patients were less than 40 years, and only 5.1 per cent were less than 30 years, whereas 40 per cent of all persons with diabetes have the disease before the age of 40 (Root, 1934). Two patients were less than 20 years old; 1 (case 3,880) had neuritis of the optic nerve and the other (case 9,230) may have had poliomyelitis and not neuritis. This low incidence in young persons may be associated not only with the low incidence of vascular disease but also with the incomplete development of the myelin sheaths, since Moore and his co-workers (1927) noted in their experiments that neuritis did not appear in young rats until the time when the myelin should be fully laid down. Careful study of all cases of neuritis in young persons with diabetes should be worth while. Marton (1929) observed that both diabetic and nondiabetic persons showed decreased nerve-muscle irritability in proportion as the age increased.

Duration, Severity and Control of the Diabetes: The duration of diabetes at the onset of the neuritis varied markedly. Four patients had neuritic symptoms before the apparent onset of the diabetes, and in 7 others there was a simultaneous onset of the two conditions. Buzzard (1890) reported a case in which thirst and polyuria supervened during the course of neuritis. In 1 of my cases the diabetes had existed for twenty-nine years before the neuritis was noted. The average duration of the diabetes prior to the onset of neuritis in the 120 cases was five and nine-tenths years, and in 28 cases diabetes had been present for only one year or less. In 42.2 per cent of the cases the diabetes was mild;[20] in 43.6 per cent, moderate, and in 15.9 per cent, severe. In 35.9 per cent of the cases glycosuria was not present (based on tests carried

20. The mild cases were those in which the usual daily dose of insulin was from 0 to 9 units, the moderate cases, those in which the usual daily dose of insulin was from 10 to 29 units and the severe cases, those in which the usual daily dose of insulin was 30 units or more. All the patients were on an adequate diet with the diabetes controlled.

out in the hospital or reported by patients) prior to the onset of the neuritis, and in 11.7 per cent more there was only slight glycosuria, a total of 47.6 per cent in which the diabetes was at least fairly well controlled. Furthermore, in 50 per cent of the cases in which I could judge the effect of regulation of the diabetes, there was no apparent effect on the neuritis; but it must be stated that controls were not used. A slight benefit resulted in 21.7 per cent. In some cases control of the diabetes did not cause apparent benefit, even over a period of months. It is difficult to believe that hyperglycemia alone causes this neuritis, although Marton (1929) noted decreased nerve-muscle irritability in proportion as the sugar content of the blood rose and the duration of the diabetes increased. The early experiments, with the exception of Grube's, bore out this statement. Kraus (1920) expressed the opinion that the severity of the diabetes was of importance but not the duration. Harris (1922) expressed the opinion that neither ketones nor sugar was the cause. Herschmann (1932) reported neuritis in cases of latent diabetes similar to that in my case 10,582. There must be some factor, as yet unknown, that gives rise to diabetic neuritis. The fact that one observes neuritis so often in diabetic patients is fairly good evidence that diabetes in some way causes neuritic changes.

Cholesteremia: The fact that the lipoid myelin sheaths of the nerves bear the brunt of the attack suggests that the disturbed fat metabolism of diabetic persons may be connected with the neuritis. Certainly frank acidosis was not an important factor in this group of cases. The cholesterol content of the blood was determined in 44 cases, but unfortunately one cannot always make an examination at or before the beginning of the neuritis. When carried out subsequently, it may give an erroneous idea because of the upset in the diabetes that is likely to be caused by severe neuritis or it may be a false value caused by the previous institution of diabetic treatment. The values in my cases ranged from 120 to 445 mg., with an average of 233.8 mg., the normal being not more than 230 mg. Values above 230 mg. were obtained for 52.3 per cent of the patients examined, but 1 of the patients had nephritis with edema. In studying the relationship between neuritis and fat metabolism I have collected diabetic nerves for analysis in the laboratory of Dr. William R. Bloor. The lipoid constituents show definite abnormalities, which are being reported in the ARCHIVES OF INTERNAL MEDICINE.

Dehydration: The upset in water balance, with resulting dehydration, occurring in untreated diabetic persons might be considered to exert some influence, but in 84.8 per cent of the cases there was no obvious dehydration. One patient (case 10,216) obtained no relief from the pains when saline solution was administered intravenously at the beginning of diabetic treatment. One frequently observes diabetic patients

with marked dehydration and no neuritic symptoms, and in 1 such patient neuritis developed after dehydration was entirely relieved.

Arteriosclerosis: Arteriosclerosis is associated with many neurologic conditions [21] and seems to play a causative rôle. It involves the peripheral [22] as well as the central nervous system. In diabetic persons the legs are markedly affected by arteriosclerosis but, as Morrison and Bogan (1929) pointed out, seldom when the patient is less than 40 years of age. If one assumes that arteriosclerosis is a factor in the production of diabetic neuropathy, the observations of Morrison and Bogan are compatible with mine, that neuritis and degenerative lesions usually affect the legs and occur rarely in diabetic persons less than 40 years old. As early as 1893 Pryce suggested extensive vascular disease as one of the causes of diabetic neuritis. Rimbaud (1909) entertained a similar idea, and Woltman and Wilder (1929) expressed the opinion that arteriosclerosis is the most important cause. Many times one notes in the literature the association of arteriosclerosis and this neuropathy. Marinesco (1901) noted thickening of the walls of the intraneural vessels. The 3 diabetic patients with paralysis whose cases were reported by Root (1922) all had arteriosclerosis.

Among the 120 cases in this group, arteriosclerosis was present in all except 9 (7.5 per cent), although it was only slight in 7 cases. Disease of the coronary vessels was present in 20 per cent, and in 30.8 per cent there was evidence of angina pectoris, apoplexy or a circulatory condition of the feet requiring surgical intervention. Of the 9 cases without arteriosclerosis, there was no pulsation in the dorsalis pedis artery in 2, and in 1 of these the oscillometer needle showed diminished excursion at the level of the left calf. One patient was a man of 39 years, who had had diabetes for two years. The fourth was a woman of 50 years with diabetes, and she may have had arteriosclerosis which was not disclosed by palpation of the radial artery. The fifth and sixth cases were the 2 discussed as possible cases of poliomyelitis. The seventh patient was the boy with neuritis of the optic nerve. The eighth was a man of 35 years with diabetes of twelve years' duration and some obvious but undiagnosed infection that may possibly have been similar to the infectious neuritis recently described by Taylor and McDonald (1932). Furthermore, there was evidence of some impairment of the circulation in the legs. The last patient (case 7,538) was a woman 21 years old who had had diabetes for five years. Neuritic pain was promptly relieved by diabetic treatment, but sluggish activity of the

21. Woltman (1921). Price (1929). Wright (1924). Critchley (1931). Bing (1932).

22. Schlessinger (1895). Franceschi (1903). Woltman (1921). Price (1923). Priestley (1931). Alpers and Wolman (1931).

reflexes persisted. The youth of 18 years (case 5,932) in the hyperglycemic group, in whom sluggish reflexes developed subsequently, was suffering from active pulmonary tuberculosis as well as from uncontrolled diabetes.

It is not sufficient to examine only one artery to determine the presence of sclerosis. At times the sclerosis is much more advanced in one site than in another. In case 10,100 there was only slight detectable sclerosis in the radial arteries, yet roentgenograms showed sclerosis of 4 plus degree in the legs. Similarly, in case 4,458 there was only slight sclerosis in the optic fundi, yet sclerosis of 4 plus degree was present in the legs. Even in the same artery, the sclerosis varies in degree at different places. A cursory examination is sometimes misleading; but, even considering this, I noted moderate or advanced arteriosclerosis in 86.7 per cent of the cases. Evidence of impaired circulation in the legs, as judged by the methods recommended by McKittrick and Root (1929), was present at least to a slight extent in 65.8 per cent of the cases in which a test was made.

Of the 120 cases there were 5 in which there was no evidence of vascular disease either by signs of arteriosclerosis or by defective circulation in the legs. The absence of detectable vascular disease in these 5 cases indicates either that arteriosclerosis is not the only cause of diabetic neuritis or that the condition in these cases was not diabetic neuritis. Other evidence against the theory that arteriosclerosis is the chief cause of diabetic neuritis is found in the relative rarity of neuritis in elderly nondiabetic patients with arteriosclerosis. In 10 cases in patients 70 years or more of age there were no neuritic symptoms and the knee jerks were normal. The ankle jerks were normal in 9 cases. In the tenth case the right ankle jerk was sluggish and the left absent. Sensation to pinprick was normal in the 2 cases tested. These findings are compromised by the fact that I have not made studies on a large group of cases, but certainly they are at variance with my findings in diabetic patients of similar age or with a similar degree of sclerosis. Even among diabetic patients sclerosis does not invariably produce manifestations of neuritis. Even when the sclerosis is so advanced that the feet and lower portion of the legs are dusky red, there may be no evidence of neuritis. In 5 such cases recently observed the only evidence of neuritis was sluggishness of the ankle jerks in 1 case. Deficient circulation probably plays its part in addition to the sclerosis. It seems to cause hypesthesia, which was well shown in case 4,319. The patient had hyperesthesia of the leg from the hip downward to the middle of the lower part of the leg, where there was a gradual transition to the hypesthesia existing below this level, and this hypesthesia coincided with the dusky area caused by impaired circulation. But that

hypesthesia is not due solely to the vascular disease is indicated by the experience of surgeons who have noted insensitivity to a much greater extent in patients with diabetic gangrene than in nondiabetic patients.

The fact that the symptoms appear rather suddenly and that the signs as well as the symptoms improve or even disappear is no proof that arteriosclerosis is not a cause. The optic neuritis in the case reported by Alpers and Wolman (1931) disappeared clinically, although the sclerosis of the vessels had advanced so far by the time of death that the optic nerves were cut almost in two by the compression. Furthermore, it is known that the signs of apoplexy disappear and that retinal hemorrhages are absorbed spontaneously (Genet, 1927). An abrupt onset of pain, such as occurred in case 9,078, may be explained by a hemorrhage involving the nervous system. The indefinite and widespread nature of the neuropathy and the patchy distribution of the pathologic changes described by Woltman and Wilder (1929) may be explained by such a widespread and patchy distribution of arteriosclerosis as one sees in diabetic patients. A condition of repeated multiple minute hemorrhages, such as those in a case reported by Raeder (1921), in conjunction with pressure from thickened arteries and the impairment of nutrition of the nerve tissue, may explain many of the phenomena seen in cases of diabetic neuropathy. René le Fort (1916) reported a case of neuritis, especially of the sympathetic system, in the leg caused by hemorrhage from a contusion. Ischemic neuritis has been described by Chavany (1931), and Priestley (1931) attributed to ischemia the degeneration he noted in cases of arteriosclerotic gangrene. It seems unlikely that ischemia or Volkmann's (1881) contracture plays any rôle in the production of diabetic neuritis.

One feature not easily explained is the nocturnal occurrence of the neuritic symptoms, which is true in cases of involvement of the leg, the arm and the abdomen. It occurs in young diabetic persons with symptoms of hyperglycemia and no evident vascular disease, as well as in older, arteriosclerotic patients. It occurs in phlegmatic as well as in nervous persons. If one attributes it to ischemia, how is one to reconcile it with Lewis' (1932) contention that the pain of ischemia arises from a working muscle, especially since diabetic patients obtain relief by pacing the floor? Furthermore, it must be attributed to arterial rather than to venous incompetency, for the latter condition is apt to be improved when the patient is prone; and yet many young diabetic patients without demonstrable arterial disease suffer from pain of this character. The explanation that at night all is quiet and one has the opportunity to humor one's ills hardly seems acceptable because of the difference in temperament in various patients with the symptom. Furthermore, walking around a room at night is not a well recognized

sedative. Nor does it seem reasonable that, were the pain based on an emotional state, so many patients would have such severe pain at night and not notice it during the day.

Anemia: Another aspect of ischemia is furnished by anemic persons. Van Bogaert (1927) reported a case of splenic anemia with peripheral neuritis. In the only case of severe secondary anemia in this series (case 11,253) there were also advanced arteriosclerosis and chronic infection of the leg. Pernicious anemia is a different matter. My cases had something in common with cases of pernicious anemia (Smithburn and Zerfas, 1931), but in the case of multiple neuritis with pernicious anemia reported by Robertson and Gowen (1930) spasticity and increased tendon reflexes were present, neither of which has been present in any of my cases of neuritis. Of course, combined system disease is associated with marked nervous changes: and I had 4 cases of pernicious anemia in this series. In each there was absence or sluggishness of tendon reflexes, and there were clinical features which suggested that diabetes played a part also in the production of the condition. The fact that of 46 of these cases tested achlorhydria was present in only 30.4 per cent and the average amount of free hydrochloric acid was 33.9 degrees is good evidence that the presence of pernicious anemia is not essential for the development of diabetic neuritis. As a matter of fact, the incidence of achlorhydria in unselected cases of diabetes is 39 per cent (Rabinowitch, Fowler and Watson, 1931).

Dietary Deficiency: Root and Rogers (1930) suggested that diabetic neuritis might be due to food deficiency, such as occurs in cases of beriberi. This idea has been indirectly or directly expressed by many authors for many years. Marchal de Calvi (1864) noted that a not too great restriction of the diabetic diet was more likely to give relief from sciatica than keeping the patient aglycosuric, and Althaus (1890) confirmed this. Bouchard (1884), Raven (1887), Woltman and Wilder (1929) and Schmidt (1930) noted return of the knee jerks in diabetic persons regaining proper nutrition and health. Angle (1928) reported improvement in a case of diabetic tabes in which the carbohydrate content of the diet was increased, and this occurred in my case 8,166. Nutritional polyneuritis, such as that reported by McCollum and Kennedy (1916), is well recognized as being due to a deficiency of vitamin B and is cured rapidly by the administration of vitamin B. There are some points of resemblance between it and diabetic neuritis. For example, its effect (Voegtlin and Lake, 1919) on the pupillary reactions, its tendency to affect chiefly the hindlegs of cats, its tendency to cause slight changes in the cord and more marked changes in the myelin sheaths of the nerves, especially that of the sciatic nerve, are similar to the changes wrought by diabetes. Then there is neuritis

attributed to nonspecific food deficiency (Gram, 1924; Shattuck, 1928; Wechsler, 1930). Wechsler suggested that this might be the cause of diabetic neuritis. It is known that occasionally diabetes is associated with some dietary deficiency disease (Wohl, 1926; Bitzer, 1931), and it is only reasonable to suppose that it occurs in other diabetic persons with a deficiency not severe enough to cause recognizable symptoms. Such a deficiency might be a cause of the neuritis. The course under treatment corresponds to that noted by Sugiura (1918) in birds with nutritional polyneuritis, although recovery is not usually so prompt in cases of diabetes, certainly not so prompt as that reported in cases of nutritional neuritis by Voegtlin and Lake (1919) and McCollum and Kennedy (1916). One of my patients obtained relief from neuritis in the leg within two weeks after she began taking yeast; but, while taking the yeast, there developed neuritis of the optic nerve of no known cause unless it was diabetes. Against the hypothesis of a nutritional cause is the fact that of 63 of the patients questioned about any previous abnormality in the diet only 1 admitted a definite deficiency. The patient ate very little meat, cheese and eggs, but, on the other hand, she drank a great deal of milk daily. Two other patients ate only a little meat, and 1 ate very few green vegetables. The diabetic diet is fairly rich in vitamin foods: meat, green vegetables, butter, cream, cheese and fruit. And patients on such a diet do have neuritis. Furthermore, many of the patients improve or recover without any change in diet. Still more evidence is derived from the fact that the addition of yeast, cod liver oil or liver in some form has not hastened recovery, as compared with recovery in patients not so treated. It is conceivable that the deficiency lies in the absorption or utilization rather than in the consumption. Against that are the facts that patients recover without any dietary change and that children, who have the severest and least well controlled diabetes, seldom have neuritis. An answer to the latter may lie in the supposition that the neuritis depends partly on arteriosclerosis, which is rarely severe in children. I might state that I do not call a diabetic patient a child simply because diabetes developed in his childhood. If the patient lives he will eventually become an adult and will become subject to the factors operating in adults.

Lipase: One highly hypothetic etiologic factor was suggested by the work of Brickner (1931), who found myelinolytic activity in the blood serum of patients with multiple sclerosis. Cherry and Crandall (1932) and Weil and Crandall (1932) investigated such lipolytic activity in the blood after pancreatic and after hepatic injury. The latter authors concluded that in experimental damage to the liver a neurotoxic agent is present in the blood serum. In 39 of 100 patients with diabetes Meyer (1931) noted definite laboratory evidence of hepatic dysfunction, which

occurred most frequently in the older patients in whom the diabetes had remained uncontrolled for a long time. Furthermore, he observed that the modern treatment for diabetes aids in improving hepatic function. These observations present an interesting possibility yet to be investigated.

Accessory Causes.—Insulin: Caravati (1933) reported a case of neuritis caused by insulin with numbness, tingling and pain in the legs occurring only with the use of insulin, to which the patient was sensitive. It at least gives one food for thought. I have observed patients in whom neuritis developed in the hospital immediately after the diabetes had become controlled. It was puzzling, and the insulin administered was a conceivable cause. It is well recognized that insulin causes local and general cutaneous anaphylaxis, and at times its administration is followed by hemorrhage.[23] Wohlwill (1928) observed cerebral pathologic changes which he attributed to hypoglycemia caused by insulin. Tzanck and Weismann-Netter (1929), Gordon (1932), Wilson and Hadden (1932) and Young (1932) described anaphylactic neuritis, and Campbell and Allison (1932) described cases of neuritis and urticaria. Insulin might act in such a way. The urticaria produced by insulin usually ceases within a few weeks, even when the same dosage of insulin is continued; and neuritis at times improves in a similar length of time. In 31.6 per cent of 98 cases in which I know whether or not insulin was being used at the time the neuritis began, insulin was being taken. In 2 of these cases (cases 9,230 and 10,405) neuritis was noted when the patient recovered from coma, the first time that insulin had been administered. In 6 other cases (cases 5,390, 8,962, 9,338, 9,452, 9,746 and 10,407) neuritis developed while insulin was being administered in the hospital. One of the patients was thin and confined to bed, and another was thin and had been crossing his legs. It seems likely that the foot drop and toe drop in these 2 cases resulted from pressure, as described by Woltman (1929; 1930). One patient (case 9,452) became aglycosuric in the hospital; foot drop developed at the end of his stay, and he recovered from it within two weeks. I hesitate to attribute any of these cases to insulin, and yet I can offer no better explanation.

Alcohol: Although 2 of the patients with ataxia said that they used alcohol to some extent, I did not find that alcohol was a factor of much importance in the series as a whole. I have a record of the admitted intake of alcohol in 97 cases; 79.4 per cent of the patients were total abstainers, and an additional 13.4 per cent said that they used it in only slight amounts.

23. Gudemann (1926). Henderson (1927). Neale (1928). Lawrence and Hollins (1928).

Focal Infection: A focus of infection was present in 38.5 per cent of the 104 cases about which there is a record of the presence or absence of the usual foci, but in some of these the focus had been removed some time previous to the onset of the neuritis. There seemed to be a definite association between the neuritis and the focus of infection in 3 cases (cases 8,112, 9,312 and 10,773). In 1 of these, treatment of an infection of the sinuses was followed by a rapid disappearance of the neuritis. In another, amelioration followed the extraction of an abscessed tooth. In the third case the neuritis flared up once after tonsillectomy and once after extraction for an abscessed dental formation. Whether there was a specific streptococcus present, as in the case reported by Rosenow (1916), I cannot say. In case 4,319 the neuritis followed an attack of gallstones. Other sources of infection noted in this series were perinephritic abscess and pulmonary tuberculosis. The effect of the tuberculosis is problematic. Tinel and Goldflam (1912), Tarchetti (1918), Harris (1922) and Lévy-Valensi (1925) reported cases of neuritis in tuberculous patients; but Tarchetti noted that the condition in his 10 cases was due to aconite medication. It is worthy of note that in the cases of the hyperglycemic type the only 2 cases in which there was not prompt response to diabetic treatment the patient had tuberculosis and abscessed teeth, respectively. In the cases of the neuritic type 1 of the patients having only slight arteriosclerosis was tuberculous.

General Infection: Wilson (1923) reported 2 cases of neuritis which he attributed to influenza. One of my patients (case 8,167) had neuritis associated with fever and symptoms which simulated influenza. He was 29 years old, had had diabetes for four years and had only slight arteriosclerosis. Another patient (case 10,265), a man 35 years old, had had diabetes for twelve years, and arteriosclerosis was not detectable. His neuritis was of the sensory type, with exquisite pain and hyperesthesia. It was associated with fever and leukocytosis of considerable degree. The 2 cases may be instances of the infectious type of neuritis previously mentioned, although facial paralysis was not present in either case. Syphilis was present in 3 of the 120 cases and had been present in 1 other case, with apparent recovery: In 2 of the 3 cases there was prompt response to diabetic treatment, and in all 4 cases there were features that suggested that diabetic neuritis was present in addition to the syphilitic process. It seemed improbable in any case and impossible in some that the neuritis resulted from the arsphenamine commonly used in the treatment of syphilis, although it has been known for many years that arsenic is a potential cause of neuropathy (Minor, 1889; Sézary and Chabanier, 1925).

Toxic Causes: In no case did I note plumbism or any known toxic condition. Of course, it is not easy to remember to question each

patient about the use of depilatory cream or other products which are rarely toxic, and it is possible that I have overlooked cases such as those reported by Short (1931) and Mahoney (1932). Certainly I did not recognize cases of paralysis due to Jamaica ginger, such as that reported by Harris (1930) and many others.

Orthopedic and Mechanical Causes.—Various orthopedic or mechanical causes of neuritis have been reported,[24] and among my cases are some in which the condition was probably affected by such factors. Subdeltoid bursitis, sacro-iliac strain, pressure from crossing the legs or lying in bed and inactivity or excessive use of an extremity have contributed to the neuritis. Toe drop in thin patients has followed rest in bed or crossing the legs in a number of instances. Often the neuritis involved nerves other than the nerve affected by the orthopedic condition. Conditions resembling neuritis from a subdeltoid bursitis have had features suggesting that the process was in reality diabetic neuritis or at least was affected by the diabetes; and Sergent and Kaufmann (1925) stated that in all cases of circumflex neuritis diabetes should be suspected. Occasionally the mechanical cause seemed too slight to have produced neuritis unless the patient was susceptible to neuritis on account of preexisting diabetes.

CASE 22,576.—A 45 year old man with diabetes of twelve years' duration complained of pain in the region of the shoulder joint and upper part of the arm and of difficulty in elevating the arm. The pain was much worse at night and disappeared when the patient paced the floor. There were moderate arteriosclerosis, tenderness along the course of the radial nerve and in the area of the subdeltoid muscle and normal reflexes. There was no paralysis or atrophy. The pain was similar to that experienced by patients with diabetic neuritis.

CASE 10,407.—A 55 year old man with diabetes of ten months' duration, advanced arteriosclerosis and active pulmonary tuberculosis had worn rather tightly fitting round garters for a few days early in September. About a week later, while he was attending a lecture, he sat with his right leg crossed over the left. He noticed a beginning numbness in the toes of the right foot. He thereupon reversed the position, only to notice numbness in the left foot. Associated with this, as he ascertained a few minutes later when he returned to his room, was his inability to elevate the left great toe or to spread apart the toes, as he had done earlier that day. Within a few days, passive and active exercise of the affected muscles resulted in improvement.

Miscellaneous Factors.—Occupation, fatigue and mental strain seem to have little or no effect on the causation of the neuritis, although neuritis did occasionally occur in patients at a time when they were under the strain of excessive work or responsibility. Since most of the patients lived in New England and were exposed to only one climate,

24. Guillain (1901). Rimbaud (1909). Breneman (1912). Babinski (1915). Woltman (1929, 1930). Ober (1930).

I have no data on the effect of climate, except that in a few cases the neuritis was worse in inclement weather. In some cases the neuritis began in midsummer and in others in the winter.

In summing up the etiologic data I may say that diabetic persons suffer from neuropathy of three types: (1) hyperglycemic, (2) degenerative and (3) neuritic. The first seems to be due to hyperglycemia or some closely associated condition, without regard to the presence or absence of vascular disease. The degenerative lesions seem to depend on an unknown diabetic factor and vascular disease. Although these lesions seem definitely associated with vascular disease, one must not forget that the arteriosclerosis and the neuropathy may be due to the same cause. The one may be merely an accompanying condition and may have no etiologic significance with respect to the other. Sluggish circulation in the lower part of the legs apparently leads to two symptoms, intermittent claudication and cutaneous hypesthesia, but the other symptoms noted in these cases seemed more likely to be due to arteriosclerosis. How diabetes causes neuritis, as opposed to degenerative neuropathy, is unknown. Vascular disease is usually, but not always, present. In some cases without such vascular disease infection seems to play a contributory rôle; and in all such cases a thorough examination for the secondary or precipitating cause should be made. Diabetic persons are subject to forces, such as pressure and alcohol, which produce neuritis in nondiabetic persons, but I believe that even in these cases the diabetes renders the patient more susceptible to the nondiabetic agent and modifies to some extent the type or severity of neuritis produced. Therefore, I caution my patients to avoid carefully such agents as alcohol and crossing the legs, which have been reported as causes of neuritis.

Prognosis.—As might be inferred from the reports in the literature and as Williamson (1924) emphatically stated, diabetic neuritis of itself does not cause death. Certainly none of my patients died of neuritis, and the duration of life after the onset of neuritis in my cases is already two and nine-tenths years, even though the period of this study extended over a period of only two and one-half years. Since there are no standard criteria for the diagnosis of the neuritis and I have not specified exactly what I mean by neuritis, it is impossible to give an exact prognosis. If by neuritis one means a simple hyperglycemic pain along a nerve course, the prognosis is excellent; but if by neuritis one includes all the neurologic symptoms and signs not due to another obvious cause, the prognosis is different. Furthermore, symptoms may disappear and later reappear. Are they due to the same agent as the previous attack or to a separate process? Sometimes symptoms disappear and minor signs remain. Is the neuritis cured or not? Sometimes complete inca-

pacity lasts for a few months, and then improvement occurs fairly rapidly, so that the patient can carry out the usual activities without too much discomfort or inconvenience; yet some symptoms and signs persist practically unchanged for a period of years. Can one say that the neuritis was cured and that the changes persisting are due merely to chronic degenerative changes? The question is difficult to answer. I believe that in some cases there is only the degenerative process and in others there is a separate and distinct process resembling real neuritis but that even in the latter the degenerative changes are prone to occur and thus modify the picture produced by the neuritis itself. Since there are degrees of severity of each process and no constant picture characteristic of either, it is at times impossible to state just when each process began, when it ended and what changes it produced. This being so, the difficulty of stating the prognosis for the cases with neuritis becomes obvious. Furthermore, the prognosis depends at least partially on the etiologic factors present. If the neuritis has merely a diabetic background and a definite mechanical precipitating cause, such as pressure, recovery is apt to ensue fairly promptly (in a few weeks), although it may be delayed for some months.

Prognosis for Symptoms: I agree with Parker (1928) that in general the prognosis is good, and recovery from the severe symptoms and disabling condition is almost certain. Seldom do severe symptoms persist for more than a few months. In those cases with sensory disturbance and marked hyperglycemia, improvement sometimes begins within a few days after the diabetes is regulated. In 1 case, however, the pain which began abruptly practically disappeared within thirty-six hours without any treatment. Certainly treatment has not brought about rapid recovery in the majority of cases, nor does improvement begin immediately after the institution of diabetic treatment, as Root and Rogers (1930) stated. It is discouraging to both the physician and the patient to note the slow response to treatment in many cases, especially in those in which the patient has a nervous temperament and shows psychic depression. In about 50 per cent of the cases improvement begins within two weeks after treatment is initiated, but in some relapse occurs shortly after the patient leaves the hospital. As Stewart (1925) and Root and Rogers (1930) remarked, the longer the duration prior to treatment, the longer delayed will be the improvement; but there are many exceptions to this. Major (1924) reported a case of diabetic tabes in which cure resulted in seven weeks by diabetic treatment, but he did not state that the ankle jerks returned and the sluggish pupils became normal. On the average, my patients did not yield to treatment in such a short period. In 47 of the cases, in which I may say that the neuritis has disappeared, the average duration of the neuritis after the initiation of treatment was eight-tenths year. Some patients

responded to treatment so well that they became symptom-free within from a week to ten days, and others still suffered to some extent more than two years after treatment was begun.

Prognosis for Signs: That the signs as well as the symptoms of diabetic neuritis disappear is recognized. Pitres and Marchand (1917) said that the neuritis, even in a severe form, is cured in a few months without persistent infirmities, although Fletcher (1925) stated that improvement of motor and sensory changes is unlikely. Bouchard (1884), Raven (1887), Woltman and Wilder (1929) and Schmidt (1930) reported the return of knee jerks in diabetic patients. Kraus (1920) mentioned rare improvement in the reflexes. Nölting and his associates (1926) reported a case with improvement in the knee jerks and return of the ankle jerks as the neuritis improved. In Angle's (1928) case of diabetic tabes there was improvement and the leg reflexes returned when a diet with a moderate carbohydrate content was substituted for the previous diet low in carbohydrates, and this occurred under similar circumstances in my case 8,166 in spite of persistent hyperglycemia and hypercholesteremia. Holt (1928) reported improvement in cutaneous sensitivity of the feet in a diabetic patient previously suffering from trophic changes in the feet. Marinesco (1895) noted return of the left knee jerk in a diabetic patient suffering from hemiplegia. Auché (1890) described signs of regeneration in diabetic nerves, as did Woltman and Wilder (1929) in 1 case; and Nicolescu and Raileanu (1926; 1927) noted signs of regeneration in the brains of diabetic patients. Two of my patients (cases 6,331 and 11,106)) had a normal ankle jerk on the side of hemiplegia and absence of the ankle jerk on the opposite side, but I do not know the condition of the ankle jerks prior to apoplexy. In 12 other patients there was an improvement in sluggish tendon jerks or a return of reflexes, which previously were not present. In 2 of these (cases 8,428 and 10,133) there was marked improvement in the position sense of the great toe as the neuritis improved, and in the former there was also partial recovery from cutaneous anesthesia of a part of the lower portion of the leg and foot. One patient (case 2,843) also regained sensitivity to touch. The period of improvement varied considerably. In 1 case (case 8,166), seven years after the onset of the neuritis the knee jerks, previously absent, were obtained with difficulty, and two years later they were easily elicited. Usually recovery occurs in much less time, in the course of a year or less. In 2 cases (cases 7,538 and 11,036) mere regulation of the diabetes was accompanied by return of the knee jerk and improvement in a sluggish ankle jerk, respectively. In 1 case (case 4,118) in which the neuritis was characterized by absence of the left knee jerk in April, there was a sluggish response in November of the same year and an almost normal response in May of the following year.

This change in reflexes was not accompanied by a corresponding change in the nutrition or health of the patient. Similarly in the other cases studied, the activity of the reflexes was not related to the nutrition except as the latter was influenced by the neuritis. It seems reasonable to assume that if lost reflexes and sensation return the nerves are not destroyed but merely damaged and complete recovery is possible.

Prognosis of Special Features: Moore (1921) and Francis and Koenig (1926) agreed that diabetic retrobulbar neuritis responds well to treatment. My 2 patients with neuritis of the optic nerve both recovered without special treatment. Patients with paralysis of the oculomotor nerve also improve. Collier (1930) said that in most cases recovery is complete and rapid, especially in those in which insulin is administered. My patients with paralysis of the facial nerve, deafness and abdominal symptoms improved over a period of months. No improvement in pupillary reaction has been noted. In the cases of disturbance of the bladder with only slight incontinence and no retention there is a tendency to improvement as the associated neuritis improves. In the cases with marked retention the difficulty has persisted, even for some years. The psychic depression parallels the neuritis, arising usually in the course of the neuritis and disappearing with it. The condition in the cases of diabetes with an associated psychosis reported by Laudenheimer (1896), Ingegnieros (1905), Pike (1921), Bostock (1926) and Reiter (1926) also improved with treatment for diabetes.

Treatment.—Treat the diabetes first, last and all the time. Treatment must be aggressive and persistent until the disease is controlled. Not the sugar content of the blood alone, but all the chemical conditions and the physical status, must be set right. Fletcher (1925) and Nölting and his associates (1926) expressed the belief that a persistently normal value for blood sugar is essential to recovery. The diet should contain a large amount of vitamin foods, fruits, green vegetables and dairy products. Meat, eggs and cereals are included in moderate amounts. The allowance of carbohydrate is at least 120 Gm. and not more than 200 Gm., not counting the antiketogenic portion of protein and fat.

If the neuritis arises shortly after the initiation of insulin therapy and has no other obvious cause, one should substitute a brand of insulin to which the patient is not sensitive.

Barker (1930) advised diaphoresis, regulation of the bowels, control of infectious processes, hot applications, sedatives, massage and electrical treatment. I have noted that heat, usually applied by means of an electric baker or warm baths, is the best agent for the relief of pain. Since the pain is of greatest severity at night, the treatments are given in the afternoon and late evening. In severe cases warm baths can be given during the night. Sun-baths have been of help, and 1 patient was much relieved by covering himself with sand and baking in the sun at

a beach. Warm but light bedclothes are of help, and 1 woman (case 10,216) received relief only by wrapping the entire leg in a blanket each night. Massage is at times very effective. Four of my patients thought it beneficial, but another (case 9,446) said that it increased rather than decreased the symptoms. Buerger's exercises should be prescribed for pain in the legs, or paresthesia, and poor circulation, as occasionally the exercises give marked relief even from the first trial. Paresthesia of the feet is more likely to be relieved by such exercises than by any other measure. One patient with pernicious anemia obtained relief from numbness of the hands when she soaked them daily in an astringent solution. In a recent case (case 11,075) without anemia this method was of no benefit during the seventeen days during which the patient was observed. I shall be interested to know what occurs in the future. However, it hardly seems reasonable to use a method which may decrease the sensitivity of the skin and thereby lead to a chance injury. Root and Rogers (1930) stated that absolute rest in bed is essential in the early stages of pain, a statement with which I do not entirely agree. Patients who stayed in bed did not always obtain relief, and 1 woman remained in bed for several months without relief. Many patients have learned that some exercise gives relief, and 1 patient refused to stay in bed because to do so caused severe pain. I am inclined to give the patient something to do, to apportion the day into periods of rest and some exercise, however slight. On the other hand, some patients with circulatory deficiency of the legs are considerably relieved while in bed. Salicylates and hypnotics are administered when necessary; but, knowing the protracted nature of the condition in some cases, I believe that opiates should be administered sparingly if not omitted entirely.

Electrical treatment for neuritis has been advised for many years.[25] Davies (1914) obtained good results with galvanism, and Piontkowsky (1930) noted recently that galvanism stimulates recovery in the severed sciatic nerves of guinea-pigs. My one experience with the use of the galvanic current was not happy, as the patient (case 5,841) stated that it increased his symptoms.

In the patients with paresis the condition has improved with baking and passive and active exercise of the muscles involved. For bedridden patients pillows have been used to take the pressure off the affected nerves. I shortened the stay in bed as much as possible in those cases. In 1 case (case 10,553), in which there was sensory neuritis of the external popliteal nerve, four days' rest in bed did not lead to paresis, however.

Attention to the general condition of the patient and to all special conditions, such as anemia, foci of infection and constipation, is given.

25. Althaus (1890). Somerville (1914). Martin (1926).

I believe it important that frequent contact with the patient be maintained, both to insure the proper execution of orders given and to reassure and encourage him. Patients with depression need particular attention, and a little encouragement sometimes seems more effective than much treatment. Sioli (1932) commented on the need for proper psychic handling of diabetic patients. One patient admitted that willpower did more for him than anything else. Another patient improved in the hospital, had a relapse at home for which even morphine gave little relief and yet improved rapidly in the hospital a second time without morphine and without any change in the regimen previously followed at home.

Accessory food substances have been given to some patients. Yeast alone was given in 5 cases, in 3 of which recovery followed an average duration of the neuritis of nine-tenths year, as opposed to eight-tenths year for the series as a whole. Similarly, in the 7 cases in which liver or liver extract alone was given, recovery occurred in only 1 case, and the neuritis lasted one year. Cod liver oil alone was given in 5 cases, in 2 of which recovery took place in an average of five-tenths year. Cod liver oil and yeast together were given in 7 cases, in only 1 of which cure was accomplished and after a duration of nine-tenths year. Yeast and liver together were given in 4 cases, in 2 of which recovery occurred in an average of one and five-tenths years. All three substances were given in 4 cases, in 3 of which recovery has not yet occurred, but in the fourth the patient was relieved of the pain in six weeks by wrapping the affected leg in a blanket at night. The results of this dietary treatment are too inexact and meager to warrant drawing more than a tentative, general conclusion that it is not apparent that cod liver oil, yeast or liver is necessary for recovery or even hastens recovery. In many cases recovery occurred without any such treatment. The diabetic diets and the previous diets on which the patients had lived were apparently fully adequate for normal nutrition provided the patients could utilize them. On the other hand, the evidence is not conclusive that these substances are not helpful. One cannot judge by the symptoms how severe the changes are in the nerves (Woltman and Wilder, 1929); and it is possible that the patients given these substances would have been worse without them.

Prophylactic treatment for neuritis is hardly recognized. Aggressive treatment of the diabetes is the prime factor. So far as possible the patient should be brought back to a normal state. The bedridden patient should be protected from pressure on the nerves and from too great inactivity; and all patients with diabetes should be cautioned to refrain from crossing the legs. Patients with a fracture and others for whom inactivity and immobilization are necessary must be treated with great care and must be allowed some use of the diseased part as soon

as practicable. Pressure of any sort along the course of a nerve or artery is to be avoided. Patients with pernicious anemia should be carefully watched and treated to prevent involvement of the nervous system. Removal of foci of infection and attention to the general condition of the patient may be of help.

One prophylactic feature applies to complications rather than to the neuritis itself. I have commented on the hypesthesia and the apparent ease with which the skin of many patients with hyperesthesia is damaged. The use of hot water bags, especially of the chemical type, is interdicted or is permitted only with careful supervision by a responsible person. Heat must be applied with great care, and the trimming of nails, corns and calluses must be done by a competent person who knows the susceptibility of the diabetic person to injury. One cannot forget the young man who sacrificed a toe and months of activity for the sake of a short nap. It would have been far better had he borne his pain a little longer and not resorted to the electric pad, which wrought so much damage in such a little while.

SUMMARY AND CONCLUSIONS

Two hundred and twenty-six persons with diabetes with neuritic manifestations were studied. In this series I noted manifestations of three types: (*a*) hyperglycemic, (*b*) degenerative and (*c*) neuritic.

The 34 cases of the hyperglycemic type were characterized by neuritic symptoms with almost no sign. The diabetes was uncontrolled at the onset of the symptoms in each case. Hyperglycemia and glycosuria were the only detected diabetic factors present in every case. Except in 2 cases no accessory factors were noted. Regulation of the diabetes gave relief within a few days. A more serious neuropathy developed subsequently in 4 cases.

The frequency of this neuropathy is not indicated by its proportion of the 226 cases studied. It is a common condition affecting both young and old persons with diabetes. Thirty-four cases were chosen at random from many that were observed in the clinic.

Forty-five cases of diabetes with relatively mild chronic neuropathy were observed. To these were added 27 cases considered separately as of the circulatory type at first, because of markedly sluggish circulation in the legs. There were evidences, however, of chronic lesions elsewhere than in the legs, and in etiology, manifestations and prognosis the condition seemed to be of the same type as that in the original 45 cases. Hence, the groups were combined. The outstanding symptoms were pain, cramps and paresthesia, of greatest intensity at night. The signs included hyporeflexia and areflexia, muscular paresis, tenderness of nerves and muscles, hypesthesia, abnormal pupillary reactions and paresis of the muscles of the bladder. The legs were involved more

frequently than any other part of the body. Although usually progressive over a long period of time, the neuropathy occasionally improved considerably. The process occurred in patients 40 years old or more, and arteriosclerosis was present in every case. The diabetic factor at fault was not detected. Regulation of the diabetes, use of Buerger's exercises, application of heat and prevention of lesions of the legs requiring surgical intervention constituted the chief means of treatment. As judged by sluggishness or absence of tendon reflexes of the legs, this type of neuropathy involves over 40 per cent of all diabetic patients.

One hundred and twenty cases of diabetes with relatively acute and usually severe neuropathy were studied. These represented the cases of diabetic neuritis and diabetic tabes. Among 1,000 consecutive cases of diabetes observed during a period of less than two and one-half years, there were 25 cases of neuritis. The neuropathy involved the legs in over 65 per cent of the cases. Pain, paresthesia, hyporeflexia and areflexia, muscular paresis, tenderness of the nerves and muscles, hypesthesia and hyperesthesia were the most frequent manifestations. The symptoms were much more intense at night than in the day. Fever and leukocytosis occurred not infrequently. The spinal fluid contained excess protein.

Special features included Argyll Robertson pupils, neuritis of the optic nerve, acute abdominal symptoms, paresis of the muscles of the bladder and psychic disturbances.

The neuritis affected old, rather than young, patients. The diabetic factor responsible was not detected, but hyperglycemia did not appear to be essential for the production of the neuritis. Evidence of vascular disease, primarily arteriosclerosis, was present in 95.8 per cent of the 120 cases. Although presumably playing a causative rôle, the arteriosclerosis may be the result of the diabetic factor which produces the neuropathy. Pressure was apparently a precipitating cause in a number of cases. Focal infection, alcoholism and sensitivity to insulin may have led to the neuritis in a few cases. Deficient dietary intake seemed of no significance, as judged by the dietary histories and the results of feeding accessory food substances.

The prognosis is good, marked improvement occurring within a few weeks in many cases and within a few months in most cases. Improvement in the signs, as well as in the symptoms, was noted at times. However, urinary retention in cases with paralysis of the bladder persisted indefinitely. Paresis of skeletal muscle usually improved rapidly and disappeared entirely. Abnormal tendon reflexes and cutaneous sensitivity often improved.

Diligent and persistent treatment of the diabetes should be given in all cases. Correction of any suspected causative factors should be

attempted. Buerger's exercises are beneficial in cases with circulatory deficiency. The application of heat has been my best sedative, but burns must be avoided.

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"REST" AND "ACTIVITY" LEVELS OF LEUKOCYTES IN HEALTH AND IN DISEASE

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There are three factors of importance which have a direct bearing on the pathologic significance of any given laboratory test: (1) the accuracy of the technical procedure used in the test; (2) the establishment of normal limits within which variations may occur which have no especial significance, and (3) the interpretation of the findings obtained. In establishing the normal limits attention must be given to the obtaining of a large enough aggregate of samples from a truly representative group to warrant acceptance of the limits found as a fair representation of normal variations. To be of any real importance any interpretation of an abnormal finding must be based on a sound comprehension of the pathogenesis of the disease process under consideration.

All these factors are of real importance when use is made of the leukocyte count. In a previous article [1] the fact was emphasized that a uniformity of technic is necessary. Even with careful dilution of the blood and thorough shaking after dilution, it was found advisable to take two samples from the diluted blood for counting if a more uniform result for the total leukocyte count is to be obtained. With carefully made cover slip smears the counting of at least 400 leukocytes was necessary to obtain a more nearly accurate differential count. Even with careful technic variations in the leukocytic picture were observed which led to a study of the limits to which these fluctuations could go before significance could be placed on them. The results obtained showed that a variation of 50 per cent in the total and up to 10 per cent in the differential count has to be allowed as a normal variation which had no especial significance. It was found that variations within these limits were present in persons on whom counts were taken at from five to ten minute intervals over a period of an hour or two. Such variation occurred at irregular and unpredictable periods. This led to the conclusion that the leukocytes were unevenly mixed in the circulating blood. In that study about 500 leukocyte counts on 25 care-

From the Hegeman Memorial Research Laboratory of the Metropolitan Life Insurance Company Sanatorium.

1. Medlar, E. M.: Extent of Variations in Leukocytes of Normal Individuals, Am. J. M. Sc. **177**:72 (Jan.) 1929.

fully chosen subjects were made, and I considered that the data obtained were sufficient to warrant their being accepted as a fair representation.

The presence of such variations having been established in carefully selected normal persons, it became necessary to determine whether similar variations were present in persons who were ill and, if so, whether the fluctuations might invalidate the pathologic interpretation placed on the counts. An investigation along this line was carried out on patients with tuberculosis.[2] The results obtained showed that the fluctuations in the total leukocyte counts in the patients with tuberculosis were similar to those found in normal subjects and that the variations in the differential counts were slightly less than in normal subjects. It was also found that although variations were present it was still possible to place a pathologic interpretation on leukocyte counts in patients with tuberculosis. The fluctuations observed were not sufficient to change a favorable pathologic interpretation to an unfavorable one, and vice versa.

This brief résumé of my previous publications has been made to indicate that I am fully aware of the fact that care must be used when an attempt is made to interpret the significance of such a complex phenomenon as is evidenced in the circulating leukocytic picture.

Medical literature contains an increasing number of articles which deal with investigations of the leukocytic picture found under a great variety of conditions and which give interpretations from various angles of approach. To the physiologic investigator the observations naturally revolve about the "so-called" physiologic activity of the leukocytes. To the clinician and surgeon the angle of approach is the significance of the leukocytic picture as a diagnostic aid. To the pathologist the leukocytes are of significance as a reflection of the status of the pathologic process in those conditions wherein the various types of leukocytes are known to play a prominent rôle. From whatever angle an approach to the study of leukocytic reactions is made, the fundamental phenomena that must be accepted as facts are as follows: 1. There is no such thing as an absolutely constant leukocyte level, either in the total count or in the differential percentage. 2. Fluctuations in the leukocytic picture are found to be inconsistent. 3. There must occur a fluctuation of more than 50 per cent in the total count and of over 8 per cent in the differential picture before much significance can be placed on it. Furthermore, if such a change is found it must persist in subsequent observations if any real reliance is to be placed on the deviation.

2. Medlar, E. M.: Evaluation of Leucocytic Reaction in Blood as Found in Cases of Tuberculosis, Am. Rev. Tuberc. **20**:312 (Sept.) 1929.

There has arisen a belief that the average leukocyte count is not reliable because of the fact that variations have been observed at different times of the day; after meals and after psychologic disturbances, such as sudden fright; under conditions of "rest" and of "activity," and after successive leukocyte counts on subjects at short intervals. It is certain that if the leukocyte count is to be used as a routine test it is very necessary to determine whether such variations warrant a discontinuance of the test or whether when allowance is made for the fluctuations the test may still be relied on.

One of the major problems in research that has occupied my attention since 1927 has been the study of the leukocytic reaction in patients with tuberculosis. During this period an average of 500 leukocyte counts per month have been made. These counts have been taken on patients confined strictly to bed as well as on those who have had unlimited mild exercise. With such a volume of work it has become an established routine to take the samples of blood between 8:30 and 10:00 a. m. And the variations that may occur during this interval of time have been determined by taking samples of blood from patients at ten minute intervals over this period. One factor which it did not appear to be necessary to consider has been brought up by the work of Garrey and Butler.[3] From their investigations they came to the conclusion that there are definite "rest" and "activity" levels of leukocytes. Since many of the patients examined in the present study were at rest and many others were active, it seemed desirable to determine whether the observations of Garrey and Butler would make it necessary to take into account the fact that a patient was in bed or engaged in exercise when an interpretation was placed on the type of leukocytic reaction found.

EXPERIMENTATION

In the investigations 15 members of the staff not having tuberculosis were used as controls for 37 patients with tuberculosis. During the study 854 total and 776 differential leukocyte counts were made on these subjects, or an average of about 16 per person.

The first part of the study was concerned with a comparison of the leukocytic picture after a night's rest with that when the subject had settled down to his daily routine after breakfast. Three counts at ten minute intervals were taken between 6:30 and 7:00 a. m., and a similar series was obtained between 8:00 and 9:00 a. m. on 10 members of the staff. These observations were repeated on three consecutive days. On 25 patients with tuberculosis 2 early and 2 late counts were made on two consecutive days, and in a few instances as many counts were made as on the normal subjects. The cases of the patients with tuberculosis were divided into two groups: one, 15 cases, in which an unfavorable pathologic inter-

3. (*a*) Garrey, W. E.: Basal Leukocyte Count and Physiologic Leukocytosis, Proc. Staff Meet. Mayo Clinic **4**:157, 1929. (*b*) Garrey, W. E., and Butler, V.: Digestive Leukocytosis Question, Am. J. Physiol. **100**:351, 1932.

pretation, according to the leukocytic picture, had been made, and the other, 10 cases, in which the pathologic interpretation was favorable. In the majority of instances the early samples were taken at a time when the patient had to be awakened for the tests to be made. In no instance was the subject allowed to get out of bed during this period of investigation. A total of 292 total and differential leukocyte counts were made during the study.

The results of this investigation are shown in table 1. In this table are given the distribution of the total counts, of the percentages of neutrophils, lymphocytes and monocytes and of the leukocytic indexes for the normal subjects and for the patients with tuberculosis for whom the pathologic interpretation was favorable and unfavorable, respectively, during the period of rest and of activity. At the bottom of each column is given the average total count, the average percentage and the average leukocytic index for the respective columns.

It will be noted that in each group the average total count and the percentages of lymphocytes and monocytes were higher on awakening. The average percentage of neutrophils and the leukocytic index were higher during activity. The degree of change was approximately the same in the subjects not having tuberculosis as in the patients with tuberculosis. In other words, the variations observed were independent of a pathologic process.

It will be noted that the "spread" in the leukocytic picture was greatest in the group of normal subjects. This was due in large part to the fact that 2 of the members of the group became ill during the period of investigation. One contracted severe bronchitis and the other severe diarrhea owing to indiscretion in eating. These 2 subjects account for 120 out of 192 instances in which one or another part of the leukocytic picture went beyond the normal limits of leukocyte counts.

The fact of most significance revealed by this table is that in the patients with tuberculosis in whom the disturbing factors occurring in the group of normal subjects were absent, the shift in the leukocytic index did not alter to an appreciable extent the pathologic interpretation of the leukocytic picture. The leukocytic index is a summation of the leukocytic picture as a whole. The method of obtaining and of interpreting the index has been presented in a previous communication,[4] to which the reader is referred.

The second part of the study was concerned with the "rest" and "activity" levels of the number of leukocytes during the time of the morning in which the routine leukocyte counts were taken. For this investigation 8 staff members, 8 ambulatory patients with tuberculosis and 4 patients who had clinically severe tuberculosis and consequently were confined to bed were selected. All patients were chosen without any reference to previous leukocyte counts. The clinical staff selected the patients with tuberculosis, and the members of the staff chosen had a good health record and no evidence of tuberculosis.

The procedure with all subjects was as follows: No change in the daily routine was made up to the day on which they were to be tested. On the morning

4. Medlar, E. M.: Am. Rev. Tuberc. **31**:621, 628 and 642 (June) 1935.

TABLE 1.—*"Rest" and "Activity" Levels of Leukocytes, Showing Distribution of Total Counts, Percentages of Neutrophils, Lymphocytes and Monocytes and Leukocytic Index*

Total Cell Count, Hundreds	Normal Subjects (10 Persons)		Patients with Tuberculosis: Unfavorable (15 Persons)		Patients with Tuberculosis: Favorable (10 Persons)	
	At Rest	Active	At Rest	Active	At Rest	Active
Total Leukocyte Counts						
Total	90	90	62	62	44	44
41 - 50	4	3	3	3	7	12
51 - 60	7	7	7	8	12	10
61 - 70	13	25	11	16	15	12
71 - 80	22	10	9	9	5	4
81 - 90	13	16	8	7	..	5
91 -100	12	13	10	8	1	..
101 -110	7	7	5	4	3	1
111 -120	4	6	3	5	..	..
121 -130	6	..	5	2	..	..
131 -140	1	..	1	..	1	..
141 -150	..	1	..	..	..	..
151 -160	1	1	..	..	..	..
161 -170	..	..	..	..	..	..
171 -180	..	1	..	..	..	..
Average	8,377	7,377	8,338	7,887	6,522	6,136
Neutrophils, Percentage	**Neutrophils**					
Total	90	90	62	62	44	44
31 - 35	..	..	..	..	6	2
36 - 40	6	2	..	..	7	2
41 - 45	9	3	..	..	5	7
46 - 50	14	8	..	..	8	7
51 - 55	24	12	5	..	12	11
56 - 60	18	19	11	1	6	7
61 - 65	6	12	21	11	..	8
66 - 70	5	15	18	21	..	..
71 - 75	2	10	7	20	..	..
76 - 80	4	6	..	8	..	..
81 - 85	2	..	..	1	..	..
86 - 90	..	3	..	..	..	..
Average	54.94	61.83	63.88	69.45	44.02	51.63
Lymphocytes, Percentage	**Lymphocytes**					
Total	90	90	62	62	44	44
6 - 10	2	2	2	6	..	..
11 - 15	5	6	8	7	..	..
16 - 20	2	9	16	30	..	..
21 - 25	8	17	21	14	..	6
26 - 30	14	15	10	5	6	7
31 - 35	22	25	5	..	7	10
36 - 40	27	11	..	..	10	5
41 - 45	9	4	..	..	8	10
46 - 50	..	..	..	..	7	3
51 - 55	1	..	..	..	4	3
Average	32.20	27.66	21.53	18.03	40.95	35.38
Monocytes, Percentage	**Monocytes**					
Total	90	90	62	62	44	44
0 - 5	2	10	..	9	1	7
6 - 10	71	87	42	46	30	35
11 - 15	19	3	18	7	13	2
16 - 20	..	..	2	..	..	..
Average	8.66	7.68	9.77	7.60	9.35	7.35
Leukocytic Index	**Leukocytic Index**					
Total	90	90	62	62	44	44
0 - 10	39	18	..	..	30	20
11 - 20	27	26	6	..	13	12
21 - 30	12	21	22	11	1	11
31 - 40	4	11	23	24	..	1
41 - 50	2	5	8	19	..	..
51 - 60	1	3	3	5	..	..
61 - 70	2	3	..	2	..	..
71 - 80	1	..	..	1	..	..
81 - 90	..	..	..	..	..	..
91 -100	2	3	..	..	..	..
Average	17.72	25.51	32.27	40.01	8.56	13.70

of the tests they were all given breakfast at 7:30 a. m. The members of the staff and the ambulatory patients went to the main dining room, as usual, for their breakfast and pursued the customary routine, up and about, until 8:00 a. m., when three consecutive samples were taken at ten minute intervals. At 8:30 all undressed and went back to bed. They were instructed to relax completely and, if possible, to go to sleep. During the morning 5 of the staff and 3 of the patients with tuberculosis succeeded in going into sound slumber. All cooperated very well, and there was no untoward psychologic reaction to the numerous examinations. Beginning at 9 a. m. sampling of the blood was started again and it was continued at ten minute intervals up to 11 a. m. The subjects then arose, dressed and went about their routine procedures until 11:20, when 3 more samples of blood were taken at ten minute intervals. The patients very ill with tuberculosis had their routine changed in no way except that their breakfast was served half an hour earlier than usual.

In this part of the study 380 total and differential leukocyte counts were taken. The samples of blood were all taken by competent and experienced assistants. The large majority of the differential counts were made by me, the rest being done by competent assistants.

The findings in this study are given in table 2, which shows the distribution of the total count, of the percentages of neutrophils, lymphocytes and monocytes, and of the leukocytic index for each of the three groups. At the bottom of the table is given the average for each respective column. Each group is taken as a whole because it seemed reasonable that if there happened to be a significant difference between the values for the rest period and those for the activity periods the whole group would reveal it better than a single subject.

A careful study of the data in this table shows that there was a slight but insignificant difference between the values for the rest period and those for the activity periods of the staff and the ambulatory patients. There was also a comparable change in the group of patients with tuberculosis who were constantly at rest in bed. The difference may be accounted for by the fact that 13 samples taken during the rest period were compared with 3 samples taken before and the same number taken after the rest period. Had it been possible to obtain the same number of samples for each period the differences noted would in all probability have disappeared. The leukocyte counts taken at 8 a. m. were well within normal variations of those taken at 11:20 a. m. The change that occurred in the leukocytic indexes during the three periods was not sufficient to alter the interpretation of the pathologic significance of the leukocytic picture in the patients with tuberculosis.

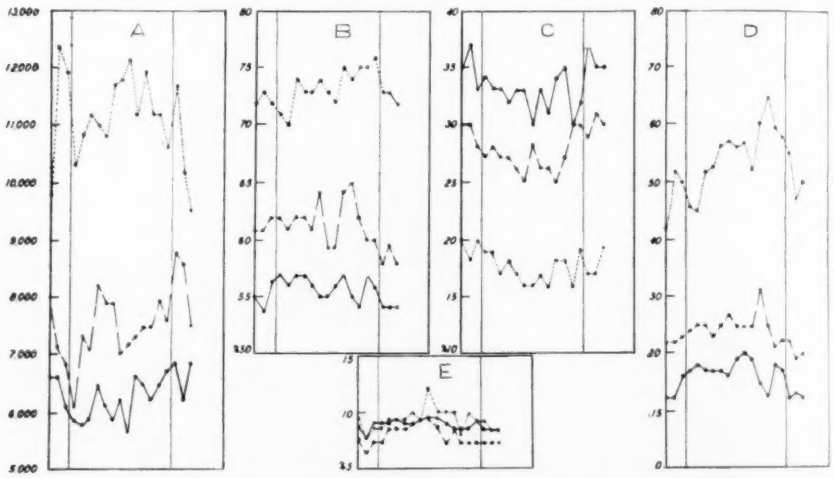
In the figure are shown the graphs for the total count, the percentages of neutrophils, lymphocytes and monocytes and the leukocytic index. These graphs represent the averages obtained for each group. The vertical lines indicate the time of retiring and of arising for the staff and the ambulatory patients. The dots in the graphs represent the ten minute intervals at which the samples of blood were taken. All of the graphs show a greater irregularity during the rest period than during

TABLE 2.—*"Rest" and "Activity" Levels of Leukocytes Showing Distribution of Total Counts, Percentages of Neutrophils, Lymphocytes and Monocytes and Leukocytic Index*

Total Cell Count, Hundreds	Normal Subjects (8 Persons)			Patients with Tuberculosis: Ambulatory (8 Persons)			Patients with Tuberculosis: Bedfast (4 Persons)		
	8:00 to 8:20 a.m.	9:00 to 11:00 a.m.	11:20 to 11:40 a.m.	8:00 to 8:20 a.m.	9:00 to 11:00 a.m.	11:20 to 11:40 a.m.	8:00 to 8:20 a.m.	9:00 to 11:00 a.m.	11:20 to 11:40 a.m.
Total Leukocyte Counts									
Total	24	104	24	24	104	24	12	52	12
31 - 40	..	4	..	..	2	..	..	..	..
41 - 50	3	26	3	3	7	..	..	..	..
51 - 60	8	17	3	2	17	4	..	..	..
61 - 70	7	32	11	5	16	3	..	4	1
71 - 80	5	20	2	5	26	3	1	9	..
81 - 90	1	3	4	5	17	5	2	4	3
91 -100	..	2	1	3	15	5	1	8	4
101 -110	..	..	..	..	..	2	2	7	..
111 -120	..	..	..	..	3	2	3	2	1
121 -130	..	..	..	..	..	..	1	4	1
131 -140	..	..	..	..	..	..	..	2	1
141 -150	..	..	..	..	..	..	..	3	..
151 -160	..	..	..	..	..	..	1	2	1
161 -170	..	..	..	..	..	..	..	2	..
171 -180	..	..	..	..	..	..	1	3	..
181 -190	..	..	..	..	..	..	..	1	..
191 -200	..	..	..	..	..	..	..	..	..
201 -210	..	..	..	..	..	..	..	1	..
Average	6,238	5,886	6,715	7,113	7,309	8,300	10,400	11,126	10,383
Neutrophils, Percentage				**Neutrophils**					
Total	24	104	24	24	104	24	12	52	12
41 - 45	..	6	3	..	..	2	..	..	..
46 - 50	8	15	3	3	20	6	..	..	..
51 - 55	4	26	9	9	23	7	..	..	..
56 - 60	6	32	8	6	25	3	..	..	..
61 - 65	6	20	1	4	17	3	2	5	2
66 - 70	..	5	..	2	5	2	3	13	2
71 - 75	..	..	..	..	7	1	2	16	3
76 - 80	..	..	..	..	2	..	4	18	5
81 - 85	..	..	..	..	..	..	1	2	..
86 - 90	..	..	..	..	..	..	..	..	..
Average	55.08	55.69	53.21	61.54	62.42	59.87	72.58	73.28	72.91
Lymphocytes, Percentage				**Lymphocytes**					
Total	24	104	24	24	104	24	12	52	12
6 - 10	..	..	..	..	..	..	2	7	..
11 - 15	..	..	..	..	6	..	2	16	6
16 - 20	..	..	..	1	16	2	3	16	3
21 - 25	..	6	..	7	20	6	2	3	1
26 - 30	7	33	3	6	25	1	3	10	2
31 - 35	8	46	11	5	28	9	..	..	..
36 - 40	8	15	7	5	9	6	..	..	..
41 - 45	1	4	3	..	..	..	..	..	..
Average	33.62	30.94	32.75	29.25	26.84	30.29	18.83	17.32	17.67
Monocytes, Percentage				**Monocytes**					
Total	24	104	24	24	104	24	12	52	12
0 - 5	3	11	..	7	6	6	2	4	1
6 - 10	21	79	24	17	89	18	10	38	10
11 - 15	..	14	..	..	9	..	..	10	1
Average	7.31	8.09	8.00	6.4	8.09	6.62	7.08	8.24	7.95
Leukocytic Index				**Leukocytic Index**					
Total	24	104	24	24	104	24	12	52	12
0 - 10	10	19	11	3	9	5	..	..	..
11 - 20	8	49	11	8	34	10	..	..	..
21 - 30	6	36	2	10	36	6	3	13	3
31 - 40	..	..	..	3	12	1	2	..	1
41 - 50	..	..	..	..	7	2	2	7	1
51 - 60	..	..	..	..	2	..	2	14	1
61 - 70	..	..	..	..	3	..	1	7	5
71 - 80	..	..	..	..	1	..	..	4	1
81 - 90	..	..	..	..	..	..	2	2	..
91 -100	..	..	..	..	..	..	..	5	..
Average	13.62	17.03	11.52	20.85	25.17	19.44	48.83	54.54	51.33

the period of activity. This comparison, however, can hardly be considered valid because of the difference in the number of the samples compared. Whatever variations are present come well within a 50 per cent fluctuation in the total and a 10 per cent change in the differential count, which I observed in healthy normal persons when samples of blood are taken at from five to ten minute intervals over a period of one to two hours. The fluctuations that occurred in the leukocytic index as shown in the graphs do not essentially alter the pathologic interpretation of the leukocytic picture for each group as a whole.

From a careful study of the records of individual subjects I gained the impression that the abnormal procedure of returning to bed after



Graphs showing the averages for: *A*, the total counts; *B*, the percentage of neutrophils; *C*, the percentage of lymphocytes; *D*, the leukocytic index, and *E*, the percentage of monocytes. The space between the vertical lines represents the time normal subjects and ambulatory patients with tuberculosis spent in bed, and the dots, the ten minute intervals at which samples of blood were taken. The solid line indicates the normal subjects, the dash line the ambulatory patients with tuberculosis and the dotted line the bedfast patients with tuberculosis.

breakfast instead of pursuing the ordinary routine brought about a greater instability of the leukocytic picture as a whole than I have observed in persons up and about at the same period of the day. In 3 instances the neutrophil count varied to as high as 15 per cent in different persons. From this it would appear to be unwise to alter radically the usual routine procedures of daily life if comparable leukocyte counts are to be obtained.

Since the data presented so far do not agree with the observations of Garrey and Butler[3b] relative to the existence of a "rest" and an "activity" level of leukocytes, total leukocyte counts were taken on the group of normal subjects at ten minute intervals between 9 and 11 a. m. on two different days while they were about their usual routine duties. The purpose of this study was to compare the leukocyte count on a day at rest with that on a day at work and also those on two different days at work. All the members of the group were available for the first day, and 6 of 8 were available for the second day at work. No attempt was made to control the activities of the persons involved, and no one knew the day on which the tests were to be made. One hundred and eighty-two total counts were taken with the subjects at their routine tasks. One assistant obtained all the samples of blood, and I made all the total counts. The results are given in table 3.

TABLE 3.—*Rest and Activity Level of Leukocytes*

	Total Leukocyte Counts (10 Minute Intervals from 9 to 11 a.m.)			
	Eight Normal Subjects		Six Normal Subjects	
Total Cell Count, Hundreds	At Work from 9 to 11 a.m.	In Bed from 8:30 to 11 a.m.	At Work from 9 to 11 a.m.	At Work from 9 to 11 a.m.
Total	104	104	78	78
31 - 40	1	4	1	..
41 - 50	18	26	14	4
51 - 60	25	17	18	9
61 - 70	21	32	17	26
71 - 80	16	20	11	12
81 - 90	16	3	11	17
91 -100	6	2	5	6
101 -110	1	..	1	4
111 -120	..	..	..	..
Average	6,236	5,886	6,204	7,242

It will be noted that there is a greater difference between the leukocyte counts on the two days at work than there is between those taken on the first day at work and those on the day in bed. None of these subjects, whether in bed or at work, showed a variation of less than 1,500 cells, and most of them showed a variation of between 2,000 and 4,000 cells. From this study it would appear illogical to attempt to compare too closely leukocyte counts of a subject from day to day. Rather it would seem that any variation of the total count within 50 per cent must be accepted as a normal variation under all conditions, whether the subject is at rest, at work or ill in bed.

COMMENT

Nature is always in a state of flux. All physiologic and pathologic processes are constantly in a state of ebb and flow. To determine with mathematical precision the point at which normal physiologic processes, that is health, cease and pathologic processes, that is disease, begin is hardly possible. Before any attempt is made to place an interpretation of abnormality on any phenomenon in life it is requisite that reason-

able limits within which a phenomenon may fluctuate be established as a normal variation. Within this range of fluctuation no definite conclusion relative to abnormality can be made. If a sample of sufficient size has been used to determine the limits of normality it will be found that the major portion of the samples obtained will lie within the central portion of the range with a decrease of the number of samples as the extreme limits are approached. Thus it will be possible to surmise that abnormality is being approached if on repeated examinations the samples remain at the extreme limits of this normal range. When on repeated examination the samples show that a phenomenon has passed definitely beyond the normal range, abnormality may be said definitely to exist.

In studies of the leukocyte count I believe that insufficient attention has been paid to the normal range of variation. There have occurred too often in the literature communications in which definite conclusions have been drawn from changes in the leukocytic picture that are well within the normal variations. Interpreting a rise of 2,000 or 3,000 cells within a few minutes following a change in posture, a sudden mild psychologic upset or some other mild and harmless incident as due to this happening is open to serious question. I do not believe that conclusions from such data are valid. At most they can be no better than surmises, because the fluctuations noted are not beyond the normal range of variation. Such interpretations have unnecessarily thrown doubt on the significance of leukocyte counts.

Variations in the total leukocyte count undoubtedly often have been misinterpreted. My observations are in agreement with those of Garrey and Butler and others, namely, that there is often a difference in the total leukocyte count in different subjects. One person may reveal total leukocyte counts ranging from 5,000 to 7,000, whereas in another the normal range may be from 7,000 to 10,000. If single total counts are taken from day to day it may happen that the number of leukocytes per cubic millimeter on one day appears to be about 3,000 cells higher than on another day. Such reasoning would undoubtedly prove erroneous if counts were made on such persons at short intervals over an hour or so each day. This is well shown in the data in table 3. Here the difference between the averages of the 6 persons on the two days at work was only 1,000 cells per cubic millimeter. And during the period of observation on each day these subjects showed a variation of from 1,500 to 3,800 cells. It was observed that there was usually a greater variation in the total cell counts in those subjects in whom the leukocyte count was the higher. I found that the higher the total counts the greater the apparent (although the same relative) variation that occurs. Thus a shift from 15,000 to 20,000 has no greater significance than a shift from

5,000 to 7,000, if the counts are taken within a few hours. Shifts of this sort, up and down, have been observed in a subject within a period of half an hour. In one subject it was the normal variation within a normal range, whereas in the other it was a normal variation within a definitely pathologic range. In either instance no importance can be placed on the change observed.

Too much attention has been centered on the total leukocyte count. It is useful to know whether there is hyperleukocytosis, ortholeukocytosis or hypoleukocytosis of the blood. This, however, is but one part of the leukocytic picture, and it often is the most insignificant. I have at my disposal over 40,000 leukocyte counts on about 600 patients with tuberculosis. The total leukocyte counts in at least two thirds of the 40,000 counts are well within a normal range of from 5,000 to 10,000. Were much reliance placed on the total leukocyte counts, one would conclude that the leukocytic picture in tuberculosis is not significant. This would be a very erroneus conclusion. In patients with tuberculosis it is of real importance to know whether definite leukocytosis or leukopenia exists. The presence of a normal total leukocyte count is not of great significance.

The differential leukocytic picture should always be considered in conjunction with the total leukocyte count. And if it is impossible to have both, which it seldom is, the differential leukocyte count should be greatly preferred to the total count. A very common experience of mine has been to find that normal total counts in different subjects have very different differential leukocytic pictures. Thus in one person a total leukocyte count of 8,000 can show 80 per cent neutrophils and 10 per cent lymphocytes, whereas in another the same total count can have a differential picture of 50 per cent neutrophils and 40 per cent lymphocytes. The difference between these two counts is significant when a pathologic interpretation is placed on them.

A considerable number of articles have appeared in journals on physiology relative to the physiologic rôle of the leukocytes. I should like to raise the query as to whether the function of the leukocytes is physiologic. If theirs is a physiologic function, do they not deal with pathologic physiology? These cells are very common participants in pathologic processes. It seems plausible that their real function, even in a normal physiologic state, is to take care of abnormal or pathologic products formed during normal physiologic processes.

To attempt to interpret the changes found between the leukocyte counts taken after a night's rest or during complete relaxation and those taken during mild and normal activity would lead at best to nothing better than conjectures. It has occurred to me that since the blood is within a closed system of vessels might not the slowing of the rate

of blood flow and a lowering of the vascular tone lead to a more sluggish circulation? Might not this allow a more irregular distribution of the leukocytic cell types? This suggestion has also been made by Garrey.[3a] If this is true, care should be exercised to procure samples of blood at a time when a normal vascular tone and blood flow are well established.

When one considers the numerous portals of entry of the leukocytes into the circulating blood, it is not surprising that fluctuations are present in the normal leukocytic picture. Nature has not provided a common collecting depot in which the leukocytes can be thoroughly mixed before they enter the main blood stream. The wonder is that the variations are not greater than they are. Even with the fluctuations as they exist, it is still possible to place valid interpretations on leukocytic reactions when allowance is made for the normal irregularity of distribution of the leukocytes in the circulating blood.

The normal variations which I have found in the leukocytic picture do not invalidate the use of the leukocyte count in interpreting pathologic processes in which leukocytes participate. I agree with the conclusion of Harvey and Hamilton,[5] who stated: "The daily variation of cell counts is not a greatly disturbing factor to their utility."

CONCLUSION

1. Definite "rest" and "activity" levels of the leukocyte count do not exist if the activity is limited to mild exercise.

2. Complete relaxation, such as a night's sleep or two hours in bed, appears to bring about a more irregular distribution of the leukocytes, both in the total and in the differential count, than is present during a state of normal activity.

3. Great care should be exercised whenever an attempt is made to interpret the significance of the leukocytic picture when the fluctuations noted are within a normal range.

4. Fluctuations occur in abnormal as well as in normal leukocytic pictures.

5. These variations, when allowed for, do not seriously interfere with the pathologic interpretation of the significance of leukocyte counts.

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5. Harvey, W. F., and Hamilton, T. D.: Constancy of Day-to-Day Leucocyte Blood Count: Medico-Statistical Study, Edinburgh M. J. **41**:465, 1934.

SERUM CALCIUM, INORGANIC PHOSPHORUS AND PHOSPHATASE ACTIVITY

IN HYPERPARATHYROIDISM, PAGET'S DISEASE, MULTIPLE MYELOMA AND NEOPLASTIC DISEASE OF THE BONES

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It is now generally recognized that the determination of serum calcium, inorganic phosphorus and phosphatase activity, in conjunction with clinical and roentgenologic study, may provide evidence of value in the differential diagnosis of certain diseases of bone. It is becoming increasingly evident, however, that for adequate interpretation of the variations in these constituents of the blood, particularly as regards their significance with respect to the underlying physiologic mechanisms involved, more data are desirable. This study is concerned with a review and appraisal of the available relevant but scattered data relating to hyperparathyroidism, Paget's disease, multiple myeloma and neoplastic disease of the bones. Additional observations on personally studied cases are presented.

METHODS

Twenty cubic centimeters of venous blood obtained from patients while fasting was transferred to a 25 cc. pyrex centrifuge tube, allowed to clot for one-half hour and then centrifugated for from five to ten minutes at 1,000 revolutions per minute. The calcium content of the serum was determined in duplicate on 2 cc. samples of the supernatant serum by the Clark and Collip modification[1] of the Kramer and Tisdall method, at least one hour being allowed for the precipitation of calcium oxalate. The inorganic phosphorus content of the serum was determined in duplicate on 1 cc. samples by the method of Kuttner and Lichtenstein,[2] with

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1. Clark, E. P., and Collip, J. B.: A Study of the Tisdall Method for the Determination of Blood Serum Calcium with a Suggested Modification, J. Biol. Chem. **63**:461, 1925.

2. Kuttner, T., and Lichtenstein, L.: Estimation of Phosphorus: Molybdic Acid-Stannous Chloride Reagent, J. Biol. Chem. **86**:671, 1930.

correction for deviation from Beer's law.[3] With serums from patients with metastatic carcinoma the filtrate obtained after precipitation of protein with 5 per cent tri-chloracetic acid was almost invariably turbid, and filtration was repeated three or four times. Even then, although hardened filter-paper and a 10 per cent solution of tri-chloracetic acid were used, it was not always possible to obtain a clear filtrate. The nature of the substance causing this cloudiness, rarely encountered in other than neoplastic conditions, was not investigated further. Serum phosphatase activity was determined in duplicate on the protein-free filtrate of a 1 cc. sample by the Bodansky method.[4] The determinations were made on serum, since oxalate diminishes phosphatase activity from 10 to 20 per cent.[5] The results were expressed in Bodansky units, a unit being defined as equivalent to 1 mg. of phosphorus in the form of phosphate ion liberated from a substrate of sodium beta-glycerophosphate during incubation for one hour at 37 C., at a p_H of 8.6.[4] When the phosphatase activity exceeded 40 Bodansky units per hundred cubic centimeters, the following positive correction was applied to the result in order to compensate for the inhibiting effect of hydrolytic products when 10 per cent or more of the substrate had been hydrolyzed:[6]

$$E_1 = E + \frac{E^2}{1{,}000}.$$

E represents the original value expressed in Bodansky units and E_1, the corrected value in Bodansky units.

The values obtained for the serum of normal adults by these methods have the following ranges: calcium content, from 9 to 11 mg. per hundred cubic centimeters; inorganic phosphorus content, from 2.7 to 4 mg.; phosphatase activity, from 1.5 to 4 Bodansky units per hundred cubic centimeters.[4] For normal children the serum phosphatase activity may be as high as 12 Bodansky units.[4]

To obviate individual variations in technic, all the determinations of calcium, inorganic phosphate and phosphatase were made by one of us (E. B. G.). In order to avoid contamination and hemolysis, we took the samples of blood in most instances with our own equipment.

The amounts of nonprotein nitrogen and, when indicated, of serum protein and bilirubin were determined by the micromethod of Folin and Wu, the macromethod of Kjeldahl and the method of Thannhauser and Andersen, respectively. These analyses were made by Miss R. Jillson.

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3. Bodansky, A.: Phosphatase Studies: I. Determination of Inorganic Phosphate; Beer's Law and Interfering Substances in the Kuttner-Lichtenstein Method, J. Biol. Chem. **99**:197, 1932.

4. Bodansky, A.: Phosphatase Studies: II. Determination of Serum Phosphatase: Factors Influencing the Accuracy of the Determination, J. Biol. Chem. **101**:93, 1933.

5. (*a*) Bodansky, A., and Jaffe, H. L.: Effects of Diet and Fasting on Plasma Phosphatase, Proc. Soc. Exper. Biol. & Med. **29**:199, 1931. (*b*) O'Reilly, T. J., and Race, J.: Osteitis Deformans, Quart. J. Med. **1**:471, 1932. (*c*) Gutman, A. B., and Gutman, E. B.: Unpublished data. (*d*) Bodansky.[4]

6. Bodansky, A., and Jaffe, H. L.: Phosphatase Studies: V. Serum Phosphatase as a Criterion of the Severity and Rate of Healing of Rickets, Am. J. Dis. Child. **48**:1268 (Dec.) 1934.

TABLE 1.—*Summary of Studies of the Blood in 4 Cases of Hyperparathyroidism*

Date	Calcium, Mg. per 100 Cc.	Inorganic Phosphorus, Mg. per 100 Cc.	Phosphatase, Bodansky Units per 100 Cc.	Nonprotein Nitrogen, Mg. per 100 Cc.	Protein, per Cent	Additional Data†
Case 1 (C. G., Male, 34 Years)						
7/14/33	15.7	2.7	34.9	..	...	
8/ 1/33	15.4	2.6	34.8	39	5.7	
8/15/33	15.8	3.1	28.3	40	6.8	Magnesium, 2.1 mg.; carbon dioxide, 47.3 volumes %; chloride, 111.1 milliequivalents; sodium, 139.5 milliequivalents; potassium, 5.1 milliequivalents
8/17/33	Operation					
8/18/33	9.7	2.4	32.1	47	...	Magnesium, 1.9 mg.
8/20/33	9.2	...	27.9	39	...	Magnesium, 2.8 mg.
8/21/33	8.8	1.9	29.9	..	..	
8/23/33	8.7	2.1	36.2	25	..	Magnesium, 3.5 mg.
8/28/33	8.1	2.7	45.6	..	...	
10/ 6/33	9.4	4.2	16.6	51	7.2	Serum cholesterol, 336 mg.
12/29/33	10.5	4.0	7.9	60	7.2	
3/16/34	10.4	4.0	6.1	60	7.0	
8/ 7/34	10.2	3.0	4.2	44	7.1	Serum cholesterol, 248 mg.
7/23/35	10.3	2.9	4.5	50	...	Serum cholesterol, 268 mg.
Case 2 (M. W., Female, 53 Years)						
				Urea Nitrogen, Mg. per 100 Cc.		
6/16/32	12.4	3.9	....	..	...	
6/30/32	13.9	5.3	....	..	7.6	
7/ 8/32*	13.1	7.1	20.2	48	...	Uric acid, 10.1 mg.; creatinine, 5 mg.
7/12/32	10.5	6.1	....	136	7.5	Creatinine, 4.6 mg.
7/20/32	8.0	5.8	....	132	...	
7/25/32	9.9	3.9	....	100	...	
7/28/32	Operation					
7/31/32	7.4	4.8	....	82	...	
8/ 1/32	6.4	4.1	....	76	...	
8/ 3/32	5.0	3.7	....	71	...	
8/ 8/32	6.1	1.7	....	65	...	
8/12/32*	8.2	2.6	11.5	64	5.9	
8/16/32	9.0	3.0	....	63	...	
8/19/32	9.6	2.9	....	64	...	
8/25/32	9.0	3.1	....	71	...	
9/ 1/32	9.6	3.4	....	73	...	
9/ 7/32	9.8	3.6	....	76		
9/12/32	9.5	3.4	....	75	...	
12/ 7/32*	9.2	3.1	13.8	..	...	
4/ 5/33*	8.9	3.9	12.1	28	6.4	Uric acid, 6.4 mg.; creatinine, 2.4 mg.
12/ 9/34	9.5	3.9	6.2	..	...	Nonprotein nitrogen, 75 mg.
12/20/35	9.0	4.1	4.7	..	...	Nonprotein nitrogen, 125 mg.
Case 3 (E. M., Female, 46 Years)						
6/19/26	11.5	2.5	....	..	...	
7/ 1/26	12.0	...	....	17	...	
Case 4 (N. P., Female, 60 Years)						
5/31/33	...	...	....	100	...	Creatinine, 3.3 mg.
6/ 5/33	9.7	...	....	..	...	
6/ 8/33*	10.2	8.4	27.3	..	..	

* Dr. A. Bodansky made the determinations indicated by the asterisk.

† Values are expressed in terms of milligrams per hundred cubic centimeters or milliequivalents per liter.

The results of analyses of the blood in 4 proved cases of hyperparathyroidism are summarized in table 1.[7] In cases 1 and 3 the characteristic findings of hypercalcemia, hypophosphatemia and increased blood phosphatase activity are presented. Cases 2 and 4, in which the amount of inorganic phosphate in the serum was increased and the calcium content was apparently normal, illustrate the effects of complicating renal insufficiency. Case 2 is of particular interest in this respect, since acute retention of nitrogen took place while the patient was under observation and the calcium level of the serum fell although no further increase in retention of phosphate was demonstrable. Case 1 illustrates also the characteristic postoperative decrease in the calcium content of the serum within twenty-four hours and the tendency of the inorganic phosphate content to remain low (or even to show a transient further decrease) for several days after operation. The blood phosphatase activity, as noted by many observers, is not immediately affected by surgical intervention but remains elevated for months or years. In case 1 a temporary increase in phosphatase activity was noted. Essentially normal values were found one year after operation. In case 2 the level of blood phosphatase was still somewhat higher than normal two and one-half years after operation. During this postoperative period the persisting elevation of blood phosphatase activity provides the only indication obtainable by studies of the blood of skeletal changes still readily apparent in roentgenograms.

A review of the literature reveals that of 156 cases of hyperparathyroidism[8] the results of determination of the serum calcium are recorded in 114. In 109 instances at least one value of 11 mg. or more per hundred cubic centimeters was obtained. In 91 cases the calcium content of the serum consistently exceeded 12 mg. Values for the amount of inorganic phosphorus in the blood are recorded in 79 cases, in 35 of which they were consistently less than 2.5 mg. per hundred cubic centimeters.

While consistent hypercalcemia with a calcium content of 12 mg. or more per hundred cubic centimeters has been found in 80 per cent of the cases of hyperparathyroidism, normal values for the calcium content may be encountered even in advanced stages of the disease. In some instances impaired renal function, as evidenced by retention of nitrogen and phosphates or by postmortem study of the kidneys, probably accounts for the apparent absence of hypercal-

7. Histories of the cases are reported elsewhere.[9]

8. This series of 156 cases of hyperparathyroidism collected from the literature includes only those in which there were definite indications of parathyroid overactivity and in which one or more parathyroid adenomas were observed at operation or autopsy.

cemia[9, 10] (cases 2 and 4). A marked decrease in the amount of calcium in the serum, associated with retention of phosphates, is a not uncommon finding in cases of terminal uremia.[11]

In other instances, however, nitrogen retention was not present, and the cause of the absence of hypercalcemia must be sought elsewhere. Bodansky and Jaffe have shown that variations in calcium intake as well as in the dosage of parathyroid extract affect the level of the calcium content of the serum in experimental hyperparathyroidism.[12] By the use of appropriate doses of parathyroid extract, they were able to produce typical lesions of osteitis fibrosa in the bones of young dogs on a low calcium intake without inducing hypercalcemia.[12] There may be analogous clinical cases of slowly progressive disease in which changes in the bone characteristic of hyperparathyroidism develop without hypercalcemia. The cases in which the values for serum calcium were normal in the earlier stages of the disease and in which hypercalcemia subsequently developed are of particular interest in this connection. The possibility that in some cases of hyperparathyroidism in which there were normal amounts of serum calcium the disease was in remission must also be considered. That depletion of available calcium reserves was not the cause of the normal values for serum calcium is suggested by the marked hypercalcemia consistently found in those cases in which extreme decalcification of the skeleton was present.

It has already been pointed out that the absence of hypophosphatemia in some cases of hyperparathyroidism may be explained by the presence of renal impairment.[10] It is uncertain whether occasional improvement in renal function after removal of a parathyroid adenoma is to be interpreted as a direct effect of the parathyroid hormone on the kidney. Hyperphosphatemia is characteristic of overdosage of parathyroid extract in some animals[13] and in man.[14]

The blood phosphatase activity in 28 cases of hyperparathyroidism with definite skeletal changes has been reported in the literature and

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9. Gutman, A. B.; Swenson, P. C., and Parsons, W. B.: The Differential Diagnosis of Hyperparathyroidism, J. A. M. A. **103**:87 (July 14) 1934.

10. Albright, F.; Aub, J. C., and Bauer, W.: Hyperparathyroidism, J. A. M. A. **102**:1276 (April 21) 1934.

11. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1931, vol. 1, p. 840. Gutman and Gutman.[5e]

12. Bodansky, A., and Jaffe, H. L.: Parathormone Dosage and Serum Calcium and Phosphorus in Experimental Chronic Hyperparathyroidism Leading to Osteitis Fibrosa, J. Exper. Med. **53**:591, 1931.

13. Thomson, D. L., and Collip, J. B.: The Parathyroid Glands, Physiol. Rev. **12**:309, 1932.

14. Albright, F.; Bauer, W.; Ropes, M., and Aub, J. C.: Studies of Calcium and Phosphorus Metabolism: IV. The Effect of the Parathyroid Hormone, J. Clin. Investigation **7**:139, 1929.

was found to be increased in every instance. The reports are summarized as follows:

				Blood			
Year	Author	Age, Years	Sex	Calcium, Mg. per 100 Cc.	Inorganic Phosphorus, Mg. per 100 Cc.	Phosphatase, Units per 100 Cc.	Increase in Phosphatase Activity
1929	Hunter[15].....	41	F	12.0-16.7	1.0-2.5	1.9 Kay[26]	Approximately 10 times normal maximum
1931	Allan[16].....	34	M	15.0-16.7	2.6-3.0	37.5-56.9 Allan (serum)[16]	4-6 times normal maximum (?)
1931	Cooley[17].....	14	F	13.6-15.2	2.6-3.0	0.25 Kay[26]?	Approximately 1¼ times normal maximum
1931	Cosin[18].....	17	M	15.3-16.5	2.2	3.1 Kay (plasma)[26]?	Approximately 15 times normal maximum (?)
1931	Hunter and Turnbull[19]	37	F	11.2-13.6	1.3	1.13 Kay (plasma)[26]	Approximately 6 times normal maximum
		49	F	14.4-15.0	1.8	1.16 Kay (plasma)[26]	Approximately 6 times normal maximum
		51	F	12.0-15.0	<2.0	1.06 Kay (plasma)[26]	Approximately 5 times normal maximum
1931	Quick and Hunsberger[20]	25	M	14.7-15.8	2.1-3.6	"Increased 4-5 fold," Kay (plasma)[26]	
1933	Dyke, Walker and Freeman[21]	14	F	17.7	2.8	42 Jenner and Kay (plasma)[27]	7 times normal maximum
1933	Keynes and Taylor[22]	18	M	14.7	1.5	0.31 Kay (plasma)[26]?	1.5 times normal maximum
1933	Rankin and Priestley[23]	47	F	10.6-11.8	2.3-3.0	61.7 Allan[16]?	Approximately 6 times normal maximum
1934	Albright, Aub Bauer[10]	13	F	12.1	4.7	36 Bodansky (plasma)[28]	9 times normal maximum
		41	F	14.2	2.3	7.5 Bodansky (plasma)[28]	Approximately 2 times normal maximum
		35	M	13.1-16.5	1.4-3.2	14.2 Bodansky (plasma)[28]	3.5 times normal maximum
		36	F	13.7	2.4	18 Bodansky (plasma)[28]	4.5 times normal maximum
		33	M	16.8	2.9	26 Bodansky (plasma)[28]	6.5 times normal maximum
		53	F	13.9	1.6	16 Bodansky (plasma)[28]	4 times normal maximum
		52	M	14.5	1.9	6.5 Bodansky (plasma)[28]	1.5 times normal maximum

15. Hunter, D.: Hyperparathyroidism (Hyperfunction of a Parathyroid Tumour in a Case of Generalized Osteitis Fibrosa), Proc. Roy. Soc. Med. (Sect. Med.) **23**:227, 1929.

16. Allan, F. N.: Hyperparathyroidism: Report of a Case, Proc. Staff Meet., Mayo Clin. **6**:684, 1931.

17. Cooley, T. B.: Hyperparathyroidism and Similar Diseases of Bone, Am. J. Dis. Child. **42**:691 (Sept.) 1931.

18. Cosin, C. F.: A Case of Osteitis Fibrosa Cystica with Cystic Adenoma of the Parathyroid, Guy's Hosp. Rep. **81**:297, 1931.

19. Hunter, D., and Turnbull, H. M.: Hyperparathyroidism: Generalized Osteitis Fibrosa, Brit. J. Surg. **19**:203, 1931.

20. Quick, A. J., and Hunsberger, A.: Hyperparathyroidism: Clinical Picture in Far Advanced Stage, J. A. M. A. **96**:745 (March 7) 1931.

21. Dyke, S. C.; Walker, R. M., and Freeman, E.: Adenoma of the Parathyroid Associated with Generalized Osteitis Fibrosa, Lancet **2**:530, 1933.

22. Keynes, G., and Taylor, H.: A Case of Parathyroid Tumour, Brit. J. Surg. **21**:20, 1933.

23. Rankin, F. W., and Priestley, J. T.: Tumors of the Parathyroid Gland, Am. J. Surg. **20**:298, 1933.

				Blood			
Year	Author	Age, Years	Sex	Calcium, Mg. per 100 Cc.	Inorganic Phosphorus, Mg. per 100 Cc.	Phosphatase, Units per 100 Cc.	Increase in Phosphatase Activity
1934	Gutman, Swenson and Parsons[6]	34	M	15.4-15.8	2.6-3.1	28.3-34.9 Bodansky (serum)[4]	7-8.5 times normal maximum
		53	F	8.0-13.9	3.9-7.1	20.2 Bodansky (serum)[4]	5 times normal maximum
		60	F	9.7-10.2	8.4	27.3 Bodansky (serum)[4]	7 times normal maximum
1935	Lahey and Haggart[24]	62	F	"Mean 13.3"	1.7-2.3	64.4 Bodansky[28]?	Approximately 16 times normal maximum
		53	F	12.5-14.9	2.2-3.0	10.2 Bodansky[28]?	"Approximately normal" (?)
		74	F	Maximum 11.3; "mean 10.0"	1.9-3.0	7.2 Bodansky[28]?	Approximately 2 times normal maximum
		44	F	14.4-15.1	2.4-3.5	35 Bodansky[28]?	Approximately 9 times normal maximum
		52	F	13.8-14.1	2.0-2.1	44.8 Bodansky[28]?	Approximately 11 times normal maximum
1935	Castleman and Mallory[25]	58	F	11.36	2.53	5.75 Bodansky[28]?	Approximately 1½ times normal maximum
		49	M	15.01	2.61	14.1 Bodansky[28]?	Approximately 3½ times normal maximum

Albright, Aub and Bauer [10] observed essentially normal levels for blood phosphatase in a group of patients presenting renal stones, hypercalcemia and diffuse hyperplasia of the parathyroids but no demonstrable changes in the bones.

In addition to the group of 156 cases of "primary" hyperparathyroidism, a state of "secondary" hyperparathyroidism has been postulated in a variety of conditions, chiefly on the basis of associated morphologic changes in the parathyroid glands or hypercalcemia. The following diseases in which complicating "secondary" hyperparathyroidism has been postulated and the evidence for the assumption are enumerated:

1. Rickets. Compensatory hypertrophy of the parathyroids,[29] compensatory hyperplasia of the parathyroids [30] and evidences of an excess

24. Lahey, F. H., and Haggart, G. E.: Clinical Diagnosis and the Operative Technique of Parathyroidectomy, Surg., Gynec. & Obst. **60**:1033, 1935.

25. Castleman, B., and Mallory, T. B.: The Pathology of the Parathyroid Gland in Hyperparathyroidism, Am. J. Path. **11**:1, 1935.

26. Kay, H. D.: Plasma Phosphatase in Osteitis Deformans and in Other Diseases of Bone, Brit. J. Exper. Path. **10**:253, 1929.

27. Jenner, H. D., and Kay, H. D.: Plasma Phosphatase: III. A Clinical Method for the Determination of Plasma Phosphatase, Brit. J. Exper. Path. **13**:22, 1932.

28. Bodansky, A.: Determination of Plasma Phosphatase, Proc. Soc. Exper. Biol. & Med. **28**:760, 1931.

29. Erdheim, J.: Rachitis und Epithelkörperchen, Vienna, Alfred Hölder, 1914.

30. Pappenheimer, A. M., and Minor, J.: Hyperplasia of the Parathyroids in Human Rickets, J. M. Research **42**:391, 1921.

of parathyroid hormone in the blood of children with rickets [31] have been described. The blood phosphatase activity is markedly increased.[32]

2. Osteomalacia. There may be compensatory hypertrophy of the parathyroids.[29] The blood phosphatase activity is moderately increased.[33]

3. Osteogenesis imperfecta. Occasional enlargement of the parathyroid glands has been described.[34] The blood phosphatase activity is normal or somewhat increased.[35]

4. Paget's disease. The evidence was summarized by Ballin.[36] The blood phosphatase activity, as is shown later, is markedly increased.

5. Multiple myeloma. Hypercalcemia and hypercalcuria with questionable hyperplasia of the parathyroid have been interpreted as indicating complicating hyperparathyroidism.[37] The blood phosphatase activity, as is shown later, is normal or slightly elevated.

6. Carcinoma with metastases to the bone. Occasional instances of hyperplasia of the parathyroids [38] and hypercalcemia, possibly due to hyperfunction of a metastasis to the parathyroids [39] have been noted. The serum phosphatase activity is discussed later.

7. Renal rickets. This disease is commonly associated with hyperplasia of the parathyroids.[40] Disturbances in the growth of the long

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31. Hamilton, B., and Schwartz, C.: Rickets and Hyperparathyroidism, Am. J. Dis. Child. **46**:775 (Oct.) 1933.

32. (*a*) Kay, H. D.: Phosphatase in Growth and Disease of Bone, Physiol. Rev. **12**:384, 1932. (*b*) Smith, J., and Maizels, M.: The Plasma Phosphatase in Rickets and Scurvy, Arch. Dis. Childhood **7**:149, 1932. (*c*) Bodansky, A., and Jaffe, H. L.: Phosphatase Studies: III. Serum Phosphatase in Diseases of the Bone: Interpretations and Significance, Arch. Int. Med. **54**:88 (July) 1934; (*d*) footnote 6.

33. Hunter and Turnbull.[19] Bodansky and Jaffe.[32c]

34. Dietrich, A.: Vergleichende Untersuchungen über Chondrodystrophie und Osteogenesis Imperfecta, Jahrb. d. in- u. ausländ. ges. Med. **322**:122, 1915. Bauer, K. H.: Ueber Osteogenesis imperfecta, Deutsche Ztschr. f. Chir. **154**:166, 1920.

35. Hunter, D.: The Significance to Clinical Medicine of Studies in Calcium and Phosphorus Metabolism, Lancet **1**:999, 1930. Kay,[32a] and Bodansky and Jaffe.[32c]

36. Ballin, M.: Parathyroidism, Ann. Surg. **96**:649, 1932.

37. Bulger, H. A.; Dixon, H. H.; Barr, D. P., and Schregardus, O.: The Functional Pathology of Hyperparathyroidism, J. Clin. Investigation **9**:143, 1930.

38. Klemperer, P.: Parathyroid Hyperplasia and Bone Destruction in Generalized Carcinomatosis, Surg., Gynec. & Obst. **36**:11, 1923.

39. Mason, R. L., and Warren, S.: Metastatic Carcinoma Simulating Hyperparathyroidism, Am. J. Path. **7**:415, 1931.

40. Langmead, F. S., and Orr, J. W.: Renal Rickets Associated with Parathyroid Hyperplasia, Arch. Dis. Childhood **8**:265, 1933.

bones, osteoporosis and granular mottling of the skull are revealed by roentgenogram.[41] The blood phosphatase activity is increased.[42]

8. Chronic nephritis. There is occasional association with compensatory (?) enlargement of the parathyroids.[43] The blood phosphatase activity is normal [44] or slightly elevated,[32a] unless changes in the bone are present, as in cases of renal rickets.

9. Nephrolithiasis. Association with hypercalcemia and diffuse parathyroid hyperplasia occurs in some cases, without demonstrable changes in the bone.[10] These instances are believed to represent a separate disease entity caused by excess of a parathyrotropic substance [45] demonstrable in the urine.[46] The blood phosphatase activity in this interesting group is within normal limits.[47]

10. Pituitary basophilism. The occasional association of this disease with parathyroid hyperplasia [48] and osteoporosis [49] and the parathyrotropic activity of preparations of the anterior lobe of the pituitary gland [48] have been considered evidence of "secondary" hyperparathyroidism. The blood phosphatase activity appears to be essentially normal in cases of pituitary basophilism.[50]

With the possible exception of certain cases of impairment of renal function, the enlargement of the parathyroid glands noted in association

41. (*a*) Hamperl, H., and Wallis, K.: Ueber "renale Rachitis" und "renalen Zwergwuchs," Virchows Arch. f. Path. Anat. **288**:119, 1933. (*b*) Vogt, E. C.: Renal Rickets, Am. J. Roentgenol. **30**:624, 1933. (*c*) Langmead and Orr.[40]

42. Kay.[32a] Hunter.[35] Vogt.[41b]

43. Bergstrand, H.: Parathyroideastudien: II. Ueber Tumoren und hyperplastische Zustände der Nebenschilddrüsen, Acta med. Scandinav. **54**:539, 1921. Radnai, P.: Untersuchung der Nebenschilddrüsen bei Nierenkranken, Frankfurt. Ztschr. f. Path. **46**:97, 1933. Pappenheimer, A. M., and Wilens, S. L.: Enlargement of the Parathyroid Glands in Renal Disease, Am. J. Path. **11**:73, 1935.

44. Gutman and Gutman.[5c] Kay.[32a]

45. Albright, F.; Churchill, E. D., and Castleman, B.: Hyperparathyroidism Due to a Diffuse Hyperplasia of All Parathyroid Glands Rather Than to a Parathyroid Adenoma of One Gland, J. Clin. Investigation **13**:685, 1934.

46. Hertz, S.: Demonstration of a Parathyreotropic Substance in Increased Amounts in the Urine of Patients with Hyperparathyroidism Due to Diffuse Hyperplasia of All Parathyroid Glands, J. Clin. Investigation **13**:698, 1934.

47. Albright, Aub and Bauer.[10] Castleman and Mallory.[25]

48. Hertz, S., and Kranes, A.: Parathyreotropic Action of the Anterior Pituitary: Histologic Evidence in the Rabbit, Endocrinology **18**:350, 1934.

49. Cushing, H.: The Basophil Adenomas of the Pituitary Body and Their Clinical Manifestations, Bull. Johns Hopkins Hosp. **50**:137, 1932.

50. Hare, D. C.: Two Cases of Dyspituitarism (Case 1), Proc. Roy. Soc. Med. **27**:1017, 1934. Macbeth, A., and Simpson, S. L.: Two Cases Demonstrating the Adrenogenital Syndrome, ibid., p. 404. Gutman and Gutman.[5c]

with the aforementioned heterogeneous group of diseases appears to be not autonomous but in the nature of a compensatory hyperplasia secondary to pathologic changes elsewhere. As most observers cited have pointed out, this does not necessarily imply overcompensation with the liberation of excessive parathyroid secretion sufficient to produce what might properly be called a state of hyperparathyroidism. When enlargement of the parathyroids and hypercalcemia coexist, as in cases of the nephrolithiasis syndrome described by Albright, Aub and Bauer,[19] the assumption of a state of hyperparathyroidism seems justified. But for the most part, the indicated morphologic changes in the parathyroid glands are not associated with hypercalcemia, hypophosphatemia or hypercalcuria—evidence of hyperparathyroidism which one expects except when marked renal insufficiency is present. Large, nonmalignant tumors of the parathyroids without evidence of parathyroid hyperfunction so far as skeletal changes are concerned have been described repeatedly. They appear to be analogous to nontoxic adenomas of the thyroid.

Similarly, hypercalcemia, such as occurs frequently in cases of multiple myeloma and occasionally in instances of metastatic malignant growths in the bones, does not, we believe, necessarily imply increased parathyroid activity but may well be due to rapid dissolution of bone resulting from malignant growth. With the exceptions already noted, postmortem examination has revealed apparently normal parathyroid glands in such instances (case of J. M. for example).

Nor can the increased blood phosphatase activity noted in some of the aforementioned conditions be construed as necessarily indicating parathyroid hyperfunction. The available evidence, to be presented later in the paper, suggests that the level of phosphatase in the blood is not a direct index of the degree of parathyroid activity.

PAGET'S DISEASE

Analyses of the blood were made in 76 cases of Paget's disease. This series includes instances of stages of the disease varying from the earliest demonstrable changes in the bone to the most severe and widespread skeletal involvement.[51] The cases are divided arbitrarily into four groups according to the extent of involvement of the bone, as indicated by roentgenographic examination of the skeleton. Many cases have been studied sufficiently long roentgenologically and clinically to appraise the activity of the lesions present in the bones. The results are shown in the following tabulation in which the bones involved by advanced lesions are indicated by bold face type:

51. These cases are included in a clinical and roentgenologic study of Paget's disease (Gutman, A. B., and Kasabach, H.: Paget's Disease [Osteitis Deformans]: Analysis of 116 Cases, Am. J. M. Sc., to be published).

Number	Patient	Sex	Age, Years	Serum Calcium, Mg. per 100 Cc.	Serum Inorganic Phosphorus, Mg. per 100 Cc.	Serum Phosphatase, Bodansky Units per 100 Cc.	Serum Nonprotein Nitrogen, Mg. per 100 Cc.	Bones Involved	Major Clinical Symptoms	Approximate Duration of Symptoms, Years
					Group 1: Cases of Advanced, Widespread Paget's Disease					
1	F. B.	M	66	10.4	3.4	130.3	46	**Skull, pelvis, humeri, femur,** entire spine	Deformities; gait; pain	10
2	M. B.	M	58	10.6	3.6	111.7	35	**Skull, spine, pelvis, femurs, tibias, scapulas, clavicles, humerus,** fibula	Deformities; gait; fracture	12
3	W. M.	M	65	9.7	3.3	109.9	34	**Skull, spine, pelvis, femurs, humerus,** ribs, scapula, clavicle	Deformities: gait; vision	15
4	A. O.	F	60	10.1	3.5	91.9	44	**Skull, pelvis, femur, tibia,** humerus, spine	Gait; fracture; pain	6
5	M. S.	F	64	10.4	3.4	59.5	39	**Skull, pelvis, spine, tibia,** femurs, humeri	Deformities; gait; paranoia	20
					Group 2: Cases of Advanced Paget's Disease					
6	L. M.	M	51	10.7	3.2	122.2	32	**Skull, pelvis, femurs, humeri, scapulas,** spine, clavicle	Gait; pain; deformities	10
7	J. R.	F	54	10.6	3.7	117.5	28	**Skull, femurs, spine, pelvis,** humerus	Gait; pain; vision	10
8	C. H.	F	47	10.0	3.8	109.5	32	**Skull, spine, pelvis,** one rib	Pain	2
9	J. W.	M	64	10.7	3.7	94.3	36	**Pelvis, femurs, skull, tibia,** spine, humeri, scapulas	Pain; deformities	5
10	E. M.	F	50	....	4.2	92.8	30	**Skull, pelvis,** femurs	**Deafness;** deformities	5
11	F. B.	F	55	9.8	3.9	89.9	27	**Skull, pelvis, femur**	Pain; limp	4
12	H. J.	F	65	10.1	3.3	78.4	28	**Skull, pelvis, femurs,** spine scapula	Deformity; gait	20
13	F. F.	M	69	11.0	3.2	77.6	37	**Skull, pelvis, spine, femurs**	Deafness; limp; deformities	7
14	E. T.	M	48	11.3	3.9	77.0	31	**Skull, pelvis, tibia,** femur	Pain; gait; deformities	10
15	M. H.	M	69	10.2	3.4	65.4	37	**Pelvis, spine, femurs,** skull	Pain; deformities	8
16	S. C.	F	45	11.5	2.9	63.9	35	**Skull, femur, fibula**	Fracture; pain	6
17	A. C.	M	59	10.7	3.8	62.9	46	**Spine, pelvis, humeri,** skull, tibia, clavicles, ulnas	Fracture; pain; deformity	9
18	M. E.	F	70	10.5	3.4	60.4	52	**Skull, pelvis, humerus, femurs,** tibia, tarsus, clavicles	Gait; asthenia; fracture	12
19	E. S.	F	37	9.8	3.6	57.9	25	**Pelvis, spine,** skull, scapulas	Asymptomatic	..
20	R. P.	M	53	9.7	3.4	57.9	35	**Pelvis, spine, femurs, humerus, clavicles,** ribs, scapula, skull	Deformities	6
21	H. S.	M	50	10.3	3.7	55.0	37	**Skull, pelvis, femur**	Headache; pain; gait	12
22	N. R.	F	45	9.3	3.6	51.4	29	**Skull, pelvis, tibia,** spine, femurs, humeri, clavicle	Deformity; pain; deaf	5
23	E. R.	F	63	10.0	2.9	46.8	30	**Skull, tibia,** pelvis	Pain; deformity	7
24	W. F.	M	43	10.8	3.5	45.7	..	**Pelvis, femur,** skull	Pain	2
25	J. S.	M	54	10.8	3.8	45.2	24	**Skull, pelvis**	Deformity; pain	8
26	J. M.	M	57	10.2	2.7	44.4	36	**Spine, pelvis, humerus,** femurs, scapulas	Pain	4
27	A. T.	F	70	....	3.8	40.1	44	**Pelvis,** spine, skull, femurs	Pain	5
28	J. S.	F	60	10.6	3.7	38.4	38	**Skull, femurs,** spine, pelvis	Deformities	10
29	T. M.	M	64	10.4	3.8	38.2	38	**Skull, tibia,** ribs, scapulas	Deformities	6
30	M. G.	F	63	9.6	4.5	38.2	34	**Skull, spine, pelvis,** radius, ulna, femur, humerus	Deformities; gait	12
31	S. S.	F	62	10.1	3.7	37.9	33	**Skull, spine, pelvis,** femurs	Pain; headache	3
32	J. L.	F	55	11.5	3.3	37.7	..	**Pelvis,** skull, femur	Deformity; limp; pain	10
33	H. N.	M	69	10.1	4.1	36.9	40	**Humerus, spine, pelvis,** skull, scapula	Pain; deformity	7
34	I. W.	F	58	10.1	3.8	36.5	36	**Spine, pelvis, tibia,** skull, femurs, humerus, scapulas	Pain; deformities	8

Number	Patient	Sex	Age, Years	Serum Calcium, Mg. per 100 Cc.	Serum Inorganic Phosphorus, Mg. per 100 Cc.	Serum Phosphatase, Bodansky Units per 100 Cc.	Serum Nonprotein Nitrogen, Mg. per 100 Cc.	Bones Involved	Major Clinical Symptoms	Approximate Duration of Symptoms, Years
35	M. S.	F	54	10.2	3.8	34.6	32	Tibias, pelvis, femur, skull, metacarpal	Deformities; gait; pain	8
36	S. L.	M	74	10.1	3.4	34.3	37	**Skull, femurs,** tibias	Deformities; gait	10
37	F. R.	M	59	9.9	3.5	33.7	36	**Pelvis, femurs, skull,** spine, tibia, humerus, scapulas, clavicle	Pain; deformity	5
38	H. K.	M	64	11.5	3.2	32.5	31	**Pelvis, skull,** spine, scapula	Deformities; gait	8
39	H. B.	F	74	10.5	3.2	32.1	32	**Pelvis, tibias,** femurs, skull	Pain; deformity; gait	24
40	B. D.	M	63	9.0	4.0	31.1	32	**Pelvis, skull,** femurs	Asymptomatic	..
41	W. C.	M	51	10.7	3.0	30.9	30	**Pelvis, spine, humerus,** skull, femurs, scapula	Fracture	½
42	A. L.	F	63	10.1	5.1	29.4	42	**Tibias, femurs, pelvis,** skull, spine	Fracture; gait; deformities	2
43	G. L.	M	72	9.8	3.2	26.7	28	**Pelvis,** femurs	Pain	..
44	L. A.	F	56	11.5	3.7	26.1	34	**Tibia, humerus,** skull	Fracture; gait; pain	9
45	M. S.	F	75	9.8	3.0	24.2	30	**Pelvis, femurs,** spine, scapula	Asymptomatic	..
46	H. S.	F	55	10.7	3.2	23.0	36	**Pelvis,** femur, spine	Pain	3
47	J. S.	M	59	10.8	3.6	23.0	29	**Pelvis, spine,** skull, femurs	Deaf	5
48	J. K.	M	63	11.2	3.2	19.7	38	**Skull, pelvis,** spine, femur, humerus	Dizzy spells	3
49	J. L.	F	58	11.1	3.6	16.8	34	**Femur, pelvis,** sacrum	Deformities; gait; headache	12
50	D. L.	M	78	10.5	2.8	15.0	27	**Pelvis, spine, femurs,** skull, scapulas, humeri	Gait	10
51	R. N.	M	76	9.9	3.4	9.7	32	**Femurs, pelvis,** sacrum	Fracture; deformity	2
				Group 3: Cases of Moderately Advanced Paget's Disease in One Area, in Most Instances with Early Lesions Elsewhere						
52	E. F.	F	62	9.2	3.2	53.6	37	**Skull**	Deformity; deaf	10
53	M. D.	F	58	10.1	2.5	49.1	33	**Skull**	Deformity	12
54	A. T.	F	43	10.4	3.4	20.8	30	**Skull**	Deformity	4
55	M. B.	F	54	10.9	3.3	13.8	35	Skull, humerus	Asymptomatic	..
56	J. S.	M	56	10.3	3.7	13.6	..	**Femur**	Pain; limp	5
57	J. T.	F	73	10.6	3.7	13.5	28	**Pelvis,** lumbar vertebrae	Asymptomatic	..
58	S. H.	M	45	10.6	3.2	13.1	30	**Ilium,** ischium, pubic bone on right side	Pain	¾
59	J. H.	F	55	9.9	3.5	12.2	32	**Radius,** sacrum, ilium	Deformity	5
60	A. R.	M	60	10.1	3.2	11.0	55	**Humerus,** ulna, pelvis	Fracture; pain	4
61	E. C.	F	77	9.6	3.1	9.1	26	**Pelvis,** skull	Asymptomatic	..
62	C. B.	F	32	10.7	3.2	8.5	26	Skull, ischium, femur	Pain	3
63	H. H.	M	57	10.6	3.4	8.0	38	**Pelvis,** sacrum, femur	Headache	2
64	S. F.	M	65	10.3	3.4	7.6	27	**Pelvis,** femur, skull	Pain	¼
65	C. P.	F	52	10.7	4.7	7.3	54	**Humerus,** femur, ilium	Asymptomatic	..
66	M. H.	M	69	10.6	4.1	4.1	27	**Pelvis**	Asymptomatic	..
				Group 4: Cases of Early Localized Paget's Disease						
67	E. M.	M	56	17.2	3.8	8.3	47	**Femur**	See text	
68	L. P.	F	55	11.1	3.0	7.9	56	**Ischium,** pubic bone on right side	Pain; gait	4
69	S. S.	M	48	10.4	2.8	7.5	35	Sacrum	Pain	1
70	E. G.	F	34	9.8	2.9	6.9	26	Ischium, pubic bone on right side	Asymptomatic	..
71	W. J.	M	54	9.4	2.8	5.7	30	Pelvis	Asymptomatic	..
72	T. M.	M	72	10.1	3.2	5.2	39	Pubic bone, ischium on right side	Asymptomatic	..
73	A. S.	M	49	8.7	3.3	5.0	..	Skull	Asymptomatic	..
74	W. W.	M	75	9.9	3.5	4.9	51	Skull	Asymptomatic	..
75	W. B.	M	70	9.5	3.0	4.5	31	Skull	Asymptomatic	..
76	E. L.	M	49	9.2	3.0	1.8	28	Ischium on right side	Asymptomatic	..

Serum Calcium.—Values within the normal range of from 9 to 11 mg. per hundred cubic centimeters were found in 65 of the 74 cases in this series, exceeding 11.5 mg. only in the following instance (case 67):

An American man, aged 57, was admitted to the Presbyterian Hospital on Feb. 11, 1933, because of a loss of 45 pounds (20.4 Kg.) in weight, increasing weakness, anorexia and vomiting for three and one-half months. He had had a dry, hacking cough for ten years, which for the preceding three months was associated with sharp pain in the right side of the chest and was intermittently productive of blood-tinged sputum. Roentgenographic examination of the chest disclosed a large cavity, with a level of fluid, in the upper lobe of the right lung. It was believed that this was an abscess of the lung, the suppuration probably being secondary to a bronchogenic carcinoma. Roentgenographic examination of

TABLE 2.—*Summary of Studies of the Blood in a Case (E. M.) of Bronchogenic Carcinoma with Incidental Localized Paget's Disease and Unexplained Hypercalcemia*

	Serum						
Date	Calcium, Mg. per 100 Cc.	Inorganic Phosphorus, Mg. per 700 Cc.	Phosphatase, Bodansky Units per 100 Cc.	Nonprotein Nitrogen, Mg. per 100 Cc.	Protein, per Cent	Carbon Dioxide, Volume per Cent	Sodium, Meq. per Liter
7/ 6/33	13.5	2.1	...	28	4.9	59	131.9
7/10/33	13.9	2.4	6.5	22	5.0	63	132.5
8/ 3/33	17.2	3.8	8.3	47	5.5		
8/16/33	18.9	4.5	10.9	40	5.7	..	133.7
8/22/33	16.4	3.9	8.7	38	5.6		

the skeleton failed to reveal metastases in the bones, but it disclosed localized Paget's disease involving the upper half of the right femur. This lesion was asymptomatic and was not suspected clinically. Loss of weight, weakness, anorexia, vomiting and intermittent fever continued, with only temporary amelioration after rib resection and drainage on July 12. Studies of the blood revealed marked hypercalcemia, the most striking of many peculiarities in the electrolytes of the serum (table 2). Roentgenograms of the entire skeleton on August 14 showed no evidence of hyperparathyroidism, multiple myeloma or metastatic malignant growth in the bones to account for the hypercalcemia. There was no apparent change in the area of Paget's disease in the right femur.

The course of the disease was progressively downward, terminating in death on August 25. Postmortem examination revealed an extensive bronchogenic carcinoma in the upper lobe of the right lung with considerable secondary suppuration. No metastases were noted. Sections of the ribs, calvarium and vertebrae were normal on histologic examination. A section from the greater trochanter of the right femur showed Paget's disease. The parathyroid glands appeared normal on gross and histologic examination. The kidneys showed a thin sub-

capsular zone of round cell infiltration; the tubules contained calcified bodies and many granular and cellular casts. The renal changes were interpreted as indicative of low grade interstitial nephritis.

It is believed that the hypercalcemia in this case was not due to the localized and relatively inactive Paget's disease but to complicating factors as yet wholly obscure.

Serum Inorganic Phosphorus.—The values in this series were within the normal range for the method employed—2.7 to 4 mg. per hundred cubic centimeters—except in 6 cases in which values of more than 4 mg. were obtained, usually associated with high normal or definitely elevated values for the nonprotein nitrogen of the serum. In 1 instance the inorganic phosphorus content of the serum was 2.5 mg. per hundred cubic centimeters.

Phosphatase Activity of the Serum.—In 75 of the 76 cases studied the activity exceeded the normal maximum value of 4 Bodansky units. A value of 1.8 Bodansky units was found in case 76, in which involvement of bone was the least extensive in the entire series. In this case discrete areas of bony condensation in the body of the right ischium, not in relation to the hip joint, were believed to be the result of early localized Paget's disease.

Our results are in general agreement wtih those reported in several recent extensive studies. Kay, Simpson and Riddoch [52] found that the value for plasma phosphatase was increased in 25 cases of Paget's disease. Their values varied from 0.4 to more than 3 Kay units, the increase in phosphatase activity being roughly proportional to the extent of involvement of the bone. The calcium content of the serum and the amount of inorganic phosphorus in the plasma were within normal limits. Bodansky and Jaffe [32e] reported values for the serum phosphatase of from 4.9 to 23.1 Bodansky units in 13 cases of localized Paget's disease and of from 50 to 125 Bodansky units in 9 additional cases of advanced polyostotic Paget's disease. In a twenty-third case in their series, the serum phosphatase activity proved to be only 15 Bodansky units, although the skeleton was extensively involved. Pathologic examination disclosed that the widespread lesions were markedly sclerosed, typical of healed lesions of Paget's disease, with little evidence of activity. The calcium content of the serum in 14 of 15 cases in which examinations were made ranged from 9.2 to 10.8 mg. per hundred cubic centimeters, and the inorganic phosphorus content in 22 of 23 cases, from 2.5 to 5 mg. In 1 case, classified roentgenologically as an instance of Paget's disease, the calcium content of the serum was 12.4

52. Kay, H. D.; Simpson, S. L., and Riddoch, G.: Osteitis Deformans, Arch. Int. Med. **53**:208 (Feb.) 1934.

mg. and the inorganic phosphorus content, 1.8 mg. O'Reilly and Race [55] found values for plasma phosphatase varying from 0.21 to 4.3 Kay units in 21 cases of Paget's disease, with the calcium content of the serum ranging from 9.1 to 11.3 and the inorganic phosphorus content of the plasma, from 2 to 3.95 mg. In 2 of these cases, in which the disease was presumed to be quiescent, the values for phosphatase were within the normal range. Roberts [53] made examinations in 13 cases and reported values for plasma phosphatase of from 6.5 to 32.1 Roberts units (the normal being about 4 units). Belden and Bernheim [54] reported the results of their determination of the calcium content of the serum in 6 cases as from 9.6 to 12.3 mg. per hundred cubic centimeters. In 3 other instances the calcium content of the serum was described as normal and in a tenth case as low. Jerome and Compere [55] in 9 cases of Paget's disease found values for the calcium content of the serum between 8.97 and 11.5 mg., and for the inorganic phosphorus content, between 2.4 and 5.7 mg. Hunter [35] in 7 cases reported values for the serum calcium of from 8.2 to 10.8 mg.; for plasma phosphate, from 3 to 3.5 mg., and for plasma phosphatase, from 0.66 to more than 1.4 Kay units. Snapper [56] reported values for serum calcium of from 9.9 to 11.5 mg. in 7 cases of Paget's disease, in 4 of which the amount of inorganic phosphorus was determined and found to vary from 2.6 to 3.4 mg.

In addition to these detailed reports, Albright, Aub and Bauer [10] referred to their results in more than 30 cases of Paget's disease; they stated that in only 1 instance did the disease seem to be complicated by hyperparathyroidism; i. e., to present hypercalcemia and hypophosphatemia. Phemister [57] remarked that in none of his 10 cases of Paget's disease was an elevation of the calcium content of the serum or a lowering of the amount of inorganic phosphorus shown. In addition to these studies, a number of isolated reports of cases of Paget's disease have appeared, which are summarized as follows (the text should be consulted for reports from the literature of more extensive series of cases [Kay,

53. Roberts, W. M.: Variations in the Phosphatase Activity of the Blood in Disease, Brit. J. Exper. Path. **11**:90, 1930.

54. Belden, H. W., and Bernheim, A.: Clinical and Therapeutic Considerations of Osteitis Deformans, Radiology **18**:325, 1932.

55. Jerome, J. T., and Compere, E. L.: The Pathological and Biochemical Changes in Paget's Disease, Illinois M. J. **64**:449, 1933.

56. Snapper, I.: Maladie osseuses et parathyroïdes, Ann. de méd. **29**:201, 1931.

57. Phemister, D. B., in discussion on Ballin.[36]

Simpson and Riddoch;[52] Bodansky and Jaffe;[32c] O'Reilly and Race;[5b] Roberts;[53] Belden and Bernheim;[54] Jerome and Compere;[55] Hunter;[35] Snapper;[56] Albright, Aub and Bauer,[10] and Phemister[57]]):

Year	Author	Patient	Sex	Age, Years	Blood: Calcium, Mg. per 100 Cc.	Blood: Inorganic Phosphorus, Mg. per 100 Cc.	Bones Involved	Comment
1924	Koechig[58]	..	..	..	12.1	...	Not specified	Calcium determined by Lyman's method
					11.8	...	Not specified	
1924	Schoen[59]	..	F	29	15.2	...	Skull, tibia, femur	
1927	Cuthbertson[60]	..	..	..	11.4	...	Skull, bones of legs, ulna	
1927	Van Hazel and Andrews[61]	J.	F	63	13.1-8.7	...	Tibia	
1928	Barrenscheen and Gold[62]	N.	..	..	13.8	...	Tibia	Calcium determined by de Waard's method
		S.	..	..	13.8	...	Femurs	
		H.	..	..	11.4	...	Humerus with sarcoma	
		K.	..	..	11.2	...	Polyostotic	
1931	Garvey[63]	S.	M	57	10.1	...	Skull, pelvis, spine, femurs	
1931	Lasch[64]	G.	M	75	12.0	3.9	Skull, tibia	Calcium determined by de Waard's method
		E.	M	67	12.2	4.1	Skull, bones of arms and legs	
		M.	F	68	11.6	4.0	Tibia	
		K.	F	56	10.2	3.9	Skull	
		M.	M	61	11.2	4.0	Skull	
1931	Welti[65]	..	..	..	"Normal"		Not specified	
1932	Berman[66]	2	F	52	11.8	3.2	Skull, legs	
		3	M	58	11.5	3.9	Skull, spine, tibias, pelvis	
		4	M	48	10.8	4.5	Skull, tibias	
1932	Jung and Hakki[67]	C.	..	56	8.8	...	Not specified	Calcium determined by Hirth's method
		O.	..	58	8.2	...	Not specified	

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67. Jung, A., and Chinassi, H. A.: Etudes sur la calcémie, Rev. de chir. Paris **51**:537, 1932.

Year	Author	Patient	Sex	Age, Years	Blood: Calcium, Mg. per 100 Cc.	Blood: Inorganic Phosphorus, Mg. per 100 Cc.	Bones Involved	Comment
1932	Kasabach and Dyke[68]	W.	F	54	13-16	4.0	Spine, humeri, pelvis, femurs, tibia	Calcium normal in 1934
		K.	M	59	11-13	...	Pelvis, spine, femurs, scapulas, humeri	
		P.	M	33	"Normal"		Skull, tibia (osteoporosis circumscripta)	
1932	Kienböck and Sereghy[69]	R.	M	64	18.0	...	Generalized	Method for calcium?
1932	Labbé et al[70].....	V.	..	..	9.7	4.0	Not specified	
		C.	..	..	8.8	2.7	Not specified	
		D.	..	..	11.4	4.8	Not specified	
1932	Laederich et al[71]..	C.	M	69	9.6	3.9	Skull, humerus, tibia, ribs, phalanges, clavicles	
1932	Laignel-Lavastine and Boquien[72]	M.	F	72	9.5-10.5	...	Generalized	
1932	Langeron et al[73]..	1	M	54	9.5	3.2	Tibias, spine, pelvis, clavicles	
		2	M	41	8.6	...	Skull, femurs, spine	
1932	Martin and Sarasin[74]	H.	M	75	10.2-11.4	4.0	Pelvis, skull, femurs	
1932	Rabinowitch[75].....	1	M	42	9.2	3.8	Femurs, humerus, rib	
1932	Santoro[76].....	D.	F	56	14.0	...	Skull, pelvis, tibias	Method for calcium?
1932	Schrijver[77].....	W.	M	82	9.6	...	Skull, tibia	
		M.	M	67	9.0	...	Skull	
1932	Schulmann and Meillaud[78]	D.	F	80	8.8	...	Skull	

68. Kasabach, H. H., and Dyke, C. G.: Osteoporosis Circumscripta of the Skull as a Form of Osteitis Deformans, Am. J. Roentgenol. **28**:192, 1932.

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75. Rabinowitch, I. M.: Metabolic Studies in a Case of Osteitis Deformans, J. Nutrition **5**:325, 1932.

76. Santoro, M.: Alterazioni pagetiche dello scheletro di una malata portatrice di grosso fibromioma calcificato, Radiol. med. **19**:712, 1932.

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Year	Author	Patient	Sex	Age, Years	Blood: Calcium, Mg. per 100 Cc.	Blood: Inorganic Phosphorus, Mg. per 100 Cc.	Bones Involved	Comment
1933	Bachmann[79].....	H.	..	56	10.8	...	Spine, pelvis, femurs	
		F.	.	48	11.0	...	Spine, femurs	
		J.	..	47	10.6	...	Skull, spine, pelvis	
1933	Colt and Lyall[80]..	1	F	54	9.8	4.5	Skull, pelvis, tibia, rib	Phosphatase, 3.96 units
1933	Benjamin and Hess[81]	..	..	60	10.7	4.7	Not specified	
1933	Körner[82].....	1	M	57	11.3	...	Skull, pelvis, ribs, bones of legs	
1933	Labbé and Petresco[83]	C.	F	68	8.8	2.7	Generalized	
1933	Stauder[84].....	E.	M	56	10.0	...	Skull, pelvis, humeri	
1933	van Bogaert[85].....	T.	M	..	10.2	3.7	Skull, tibias, femurs, spine	
		M.	M	..	9.0	...	Pelvis, femurs	
1934	Arnulf and van der Linden[86]	F.	M	63	9.0	...	Femur, pelvis, spine	
1934	Barth[87].....	1	M	59	10.0	...	Skull, pelvis, lumbar vertebrae	
1934	Gouterman[88].....	M.	M	65	18.0	3.7	Skull, pelvis (femurs ?)	Method for calcium?
1934	Haguenau et al[89]..	M.	M	62	14.2	...	"Diffuse"	Method for calcium?
1934	Levin[90].....	A.	M	63	12.0	...	Skull, humerus, femurs, pelvis	

79. Bachmann: Ein Beitrag zur Ostitis deformans Paget, Röntgenpraxis **5**: 161, 1933.

80. Colt, G. H., and Lyall, A.: A Case of Osteitis Deformans Treated with Parathormone, Brit. M. J. **2**:10, 1933.

81. Benjamin, H. R., and Hess, A. F.: The Forms of the Calcium and Inorganic Phosphorus in Human and Animal Sera: I. Normal, Rachitic, Hypercalcemic and Other Conditions, J. Biol. Chem. **100**:27, 1933.

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84. Stauder, K. H.: Psychische Störungen bei Ostitis deformans (Paget) des Schädels, Arch. f. Psychiat. **98**:546, 1933.

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Year	Author	Patient	Sex	Age, Years	Blood: Calcium, Mg. per 100 Cc.	Blood: Inorganic Phosphorus, Mg. per 100 Cc.	Bones Involved	Comment
1934	Meyer[91]	I.	M	46	9.6	3.3	Spine, pelvis, femurs, skull, humeri, tibias, radii	
1934	Rummert[92]	K.	M	31	10.2-11.4	...		
1934	Scriver and Venning[93]	K.	F	64	10.8	3.1	Skull, spine, femurs	
		A.	F	47	9.5	3.9	Skull, spine, femurs, tibias, fibulas, humerus	
		D.	M	62	8.6	3.7	Skull, pelvis, tibias, femur	
		T.	F	53	6.9-8.3	6.4	Skull, tibias, fibulas, femurs, spine	
1934	von Bonsdorff[94]	..	F	59	11.1-12.0	4.0	Tibias, skull, spine, humeri	
1934	Weibel[95]	..	F	57	8.9	1.5	Skull, spine	
1935	Robbins and Kydd[96]	4	M	64	10.2-7.6	4.7-3.7	Spine, pelvis, femur, skull, clavicle	

MULTIPLE MYELOMA

The results of analyses of the blood in 6 cases of multiple myeloma are summarized in table 3. In cases 1 and 2 the diagnosis was confirmed by postmortem examination, which in both instances revealed widespread lesions of the plasma cell type. Biopsy or autopsy was not permitted in cases 3 to 6. The diagnosis in these instances rests on the roentgenographic finding of multiple lesions of the bones, characteristic both as to appearance and localization, a typical clinical history and course and consistent laboratory findings. In each instance extensive investigation failed to reveal evidence of a primary neoplasm involving organs from which metastasis commonly takes place to the bones. The possibility of metastatic lesions from an unrecognized focus cannot be ruled out, however.

The amount of serum calcium was definitely elevated in 4 of the 6 cases in this series. In case 1 the level of the serum calcium was normal at the first examination, but it gradually rose. In case 2 the calcium

91. Meyer, H. I.: Paget's Disease (Osteitis Deformans), M. Clin. North America **17**:1533, 1934.

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95. Weibel, W.: Ueber Ostitis deformans (Paget) des Schädels mit Hörstörungen, Schweiz. med. Wchnschr. **15**:430, 1934.

96. Robbins, C. L., and Kydd, D. M.: A Note on the Metabolic Criteria of Hyperparathyroidism, J. Clin. Investigation **14**:220, 1935.

TABLE 3.—*Summary of Studies of the Blood in 6 Cases of Multiple Myeloma*

					Serum					Urine			
Number	Patient	Sex	Age, Years	Date	Calcium, Mg. per 100 Cc.	Inorganic Phosphorus, Mg. per 100 Cc.	Phosphatase, Bodansky Units per 100 Cc.	Non-protein Nitrogen, Mg. per 100 Cc.	Protein, per Cent	Albumin	Bence-Jones Protein	Roentgenographic Findings	Relevant Clinical Data
1	J. M.	M	64	1/24/34	10.5	3.7	1.7	48	...	++	+	Multiple areas of destruction of bone in ribs, lumbar and thoracic vertebrae, pelvis, femurs and scapula	Pain in back, shoulders and arm; loss of 30 lbs.; pallor; tenderness over thoracic vertebrae; terminal fever; hemoglobin, 65%; red cells, 3,100,000; death, 2/26/34; parathyroids normal
				2/ 6/34	12.0	...	...	..	9.0				
				2/27/34*	15.3	...	...	..	...				
2	A. S.	F	58	5/ 8/34†	....	...	...	..	4.0	+++	++++	Multiple areas of destruction of bone in spine, ribs, skull, pelvis, upper half of humeri and femurs	Loss of weight; pain in chest and back; pallor; cachexia; pallor and weakness; hemoglobin, 45%; red cells, 1,800,000; death, 7/5/34
				5/17/34	8.5	2.6	5.2	40	3.5				
3	D. F.	M	60	10/24/32	15.5	3.0	...	Urea 39	6.1	++	+	Multiple areas of decreased density in skull, ribs, radius, ulna and spine	Pallor; weakness; loss of 25 lbs.; pathologic fractures of ribs and humerus; dyspnea; hemoglobin, 33%; red cells, 1,300,000; death, 4/12/33
				11/ 1/32‡	16.1	3.9	4.9	..	...				
4	P. F.	M	59	10/25/33	15.7	4.9	...	..	9.0	++	+ ?	Multiple areas of decreased density in ribs, clavicles, cervical and thoracic vertebrae and scapulas; one punched-out area in femur	Pain in chest; tenderness over lumbar spine; frequency of urination; uremia; auricular fibrillation; slightly enlarged, soft nonnodular prostate; terminal fever; hemoglobin, 89%; red cells, 4,200,000; death, 10/31/33
				10/29/33	17.0	4.8	3.0	125	9.9				
5	M. C.	F	56	4/20/33#	"Normal"	3.0	5.0	15	8.3	—	—	Multiple punched-out areas in skull, spine, ribs and long bones	Pain; loss of weight; pathologic fractures; anemia; death, December 1933 .
6	A. C.	M	47	2/21/34	13.3	6.0	4.6	80	6.3	+	0	Multiple punched-out areas in ribs, scapula, pelvis and humeri	Pain in chest and neck; tenderness over ribs and spine; loss of 20 lbs.; low grade fever; hemoglobin, 78%; red cells, 4,380,000; death, 4/12/34
				3/ 1/34	13.0	3.5	5.3	65	6.9				

* The blood was obtained eighteen hours after death.
† This case occurred in the service of Dr. M. Lentz.
‡ Dr. A. Bodansky determined the values in this case.
# This case occurred in the service of Dr. Rolfe Long.

content of the serum was maintained at normal levels for several years, but decreased to 8.5 mg. per hundred cubic centimeters in the terminal stages of the disease. In the only examination of the blood made in case 5 the amount of serum calcium was normal. Essentially normal values for the amount of inorganic phosphorus in the serum were obtained, except when impairment of renal function caused an increase. The serum phosphatase activity varied from 1.7 to 5.3 Bodansky units. In cases 2, 3, 5 and 6 the value for serum phosphatase slightly exceeded the normal maximum, but in view of the extensive involvement of bone the increase was insignificant compared with values found in cases of advanced hyperparathyroidism. The protein content of the serum was somewhat increased in cases 1, 4 and 5, but it was normal in cases 3 and 6 and low in case 2. The frequent occurrence of hypercalcemia, the normal or slightly increased amount of inorganic phosphorus and phosphatase in the blood and the irregular occurrence of hyperproteinemia observed in the cases in our series are representative of the reports in the literature, a summary of which follows:

					Serum			
						Inorganic		
Year	Authors	Patient	Sex	Age, Yrs.	Calcium, Mg. per 100 Cc.	Phosphorus, Mg. per 100 Cc.	Protein, Percentage	Evidence for Diagnosis
1923	Briggs[97]	..	..	..	10.0	4.0	....	
1927	Charlton[98]	..	F	57	12.0-16.0	...	....	Autopsy
1927	Currie[99]	8.	M	59	10.0	...	....	Bence-Jones protein
1928	Belden[100]	14	F	57	15.3-18.7	2.7-3.7	....	
1928	Durman[101]	..	M	31	16.1	3.4-4.1	....	Autopsy
1928	Perlzweig et al[102]	E.	M	40	10.8	4.8	12.3-13.8	Biopsy
1929	Hewitt[103]	1	M	46	12.8	...	6.3	Bence-Jones protein
		2	F	66	9.4	...	....	Bence-Jones protein
		5	M	59	9.7	...	....	Bence-Jones protein
1929	Ohlsson and Nordh[104]	..	M	37	15.0	...	....	Bence-Jones protein
1929	Schittenhelm[105]	..	F	46	20.0-10.4	...	....	

97. Briggs, A. P.: A Study of the Inorganic Elements of Blood Plasma, J. Biol. Chem. **57**:351, 1923.

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100. Belden, W. W.: Bone Diseases, Radiology **11**:281, 1928.

101. Durman, D. C.: Myeloma of the Spine, Ann. Surg. **88**:975, 1928.

102. Perlzweig, W. A.; Delrue, G., and Geschickter, C.: Hyperproteinemia Associated with Multiple Myelomas, J. A. M. A. **90**:755 (March 10) 1928.

103. Hewitt, L. F.: Urine Proteins in Nephrosis, Pregnancy and Myelomatosis, Lancet **1**:66, 1929.

104. Ohlsson, E., and Nordh, G.: Der Tryptophangehalt in Bence-Jones-Eiweiss, Biochem. Ztschr. **215**:440, 1929.

105. Schittenhelm, A.: Multiple Myelom (Kahlersche Krankheit), Deutsche med. Wchnschr. **55**:508, 1929.

Year	Authors	Patient	Sex	Age, Yrs.	Serum: Inorganic Calcium, Mg. per 100 Cc.	Serum: Inorganic Phosphorus, Mg. per 100 Cc.	Serum: Protein, Percentage	Evidence for Diagnosis
1930	Barr and Bulger[106]	3	F	46	16.0-17.8	3.7	....	Autopsy (patient at St. Louis City Hospital)
1930	Perla and Hutner[107]	1	M	43	13.4-14.6	6.2	....	Autopsy
1930	Smith[108]	..	..	..	....	...	....	"Two cases with hypercalcemia"
1930	Soper and Stroud[109]	..	..	..	....	...	....	"One case with hypercalcemia"
1931	Center and Merar[110]	..	M	70	7.0	...	....	Bence-Jones protein
1931	Jores[111]	1	M	57	12.4-15.4	4.1-2.2	....	Autopsy
		2	F	48	18.2-20.2	3.5-4.0	9.3	Bence-Jones protein
1931	Snapper[112]	1	..	..	15.4	4.3	....	
		2	..	..	12.0	5.2	....	
		3	..	..	10.1	5.6	....	
		4	..	..	12.5	5.2	....	
		5	..	..	11.8	2.8	....	
1931	Turner[113]	..	..	..	13.2	3.4	6.56	
1932	Ask-Upmark[114]	..	..	..	....	...	....	"Normal calcium in several cases"
1932	Aub and Farquharson[115]	M.	F	27	10.4-9.8	3.6-3.4	....	Biopsy
1932	Freund and Magnus-Levy[116]	E.	M	52	11.6	...	<6.0	Bence-Jones protein
1932	Green[117]	..	M	48	"High"	"High"	....	
1932	Mainzer[118]	..	M	46	11.9-12.5	4.8-6.8	7.4-7.2	Autopsy
1932	Reimann[119]	N.	M	46	18.0	...	10.1	Autopsy

106. Barr, D. P., and Bulger, H. A.: The Clinical Syndrome of Hyperparathyroidism, Am. J. M. Sc. **179**:449, 1930.

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111. Jores, A.: Beitrag zur Differentialdiagnose des multiplen Myeloms und der Ostitis fibrosa generalisata, Klin. Wchnschr. **10**:2352, 1931.

112. Snapper, I.: Calcium and Inorganic Phosphates of the Serum in Hyperparathyroidism and Myeloma, Acta brevia neerland. **1**:25, 1931.

113. Turner, R. H.: The Pathologic Physiology of Pellagra: III. The Serum Calcium and Phosphorus, With Especial Reference to Nervous Symptoms, J. Clin. Investigation **10**:87, 1931.

114. Ask-Upmark, E.: Beitrag zur Differentialdiagnose des multiplen Myeloms und der Ostitis fibrosa generalisata, Klin. Wchnschr. **11**:288, 1932.

115. Aub, J. C., and Farquharson, R. F.: Studies of Calcium and Phosphorus Metabolism: XV. In Various Metabolic and Bone Diseases, J. Clin. Investigation **11**:235, 1932.

116. Freund, R., and Magnus-Levy, A.: Multiple Myelome: V. Ueber Besonderheiten der Blutzusammensetzung, Ztschr. f. klin. Med. **121**:1, 1932.

117. Green, T. M.: Multiple Myeloma, South. Med. & Surg. **94**:513, 1932.

118. Mainzer, F.: Bence-Jonessche Proteinurie und Nierenfunktion, Ztschr. f. klin. Med. **119**:363, 1932.

119. Reimann, H. A.: Hyperproteinemia as a Cause of Autohemagglutination, J. A. M. A. **99**:1411 (Oct. 22) 1932.

Year	Authors	Patient	Sex	Age, Yrs.	Serum: Calcium, Mg. per 100 Cc.	Serum: Inorganic Phosphorus, Mg. per 100 Cc.	Serum: Protein, Percentage	Evidence for Diagnosis
1932	Shirer et al.[120]	1	M	64	12.2-15.5	2.6-8.0	10.0-13.8	Phosphatase, 0.12 Kay units; autopsy
		2	F	49	11.2	4.3	11.4-10.0	Bence-Jones protein
1932	Slavens[121]	..	M	4	"Normal"	"Normal"	....	Biopsy (plasmocytoma ?)
1932	Wirth[122]	H.	M	51	13.2	3.4	6.6	
1933	Bell[123]	81	M	59	10.9-15.8	...	5.9	Autopsy
		83	M	51	18.2	...	6.5	Autopsy
		86	M	52	"Normal"	...	....	Autopsy
1933	Bulger and Gausmann[124]	8.	..	..	13.5-18.1	6.8-6.2	....	
	(Case 27,621)	..	..	..	16.5-16.9	4.0-4.9	....	
1933	Caylor and Nickel[125]	..	F	52	8.0-19.5	3.5-4.0	....	Biopsy
1933	Chester[126]	1	M	46	11.0	4.2	4.7	Autopsy
		2	F	55	"Normal"	...	4.7	Bence-Jones protein
1933	Ellermann and Schrøder[127]	..	M	42	10.8	...	...	
1933	Herbert[128]	Ho.	F	54	16.9	4.2	12.6	Autopsy
		H.	M	55	10.6	4.7	6.5	
1933	Langeron et al.[129]	D.	M	55	9.8	...	....	Biopsy
1933	Lenshoek[130]	2	M	61	11.8-12.2	3.7-4.7	8.3	Biopsy
1933	Magnus-Levy[131]	D.	M	56	10.6	...	6.5	Bence-Jones protein
		F.	F	64	8.6	...	7.3	Autopsy
		B.	F	46	12.3	...	9.9	Autopsy
		P.	F	50	11.9	3.2	13.0	Bence-Jones protein
		H.	M	64	13.3	...	12.0	Autopsy
		V_1	F	59	11.0	...	13.6	Autopsy
		V_2	M	59	15.9	...	10.0-12.1	Autopsy

120. Shirer, J. W.; Duncan, W., and Haden, R. L.: Hyperproteinemia Due to Bence-Jones Protein in Myelomatosis, Arch. Int. Med. **50**:829 (Dec.) 1932.

121. Slavens, J. J.: Multiple Myeloma in a Child: Report of a Case, Proc. Staff Meet., Mayo Clin. **7**:687, 1932.

122. Wirth, W. R.: Multiple Myeloma: Report of a Case, New Orleans M. & S. J. **84**:698, 1932.

123. Bell, E. T.: Renal Lesions Associated with Multiple Myeloma, Am. J. Path. **9**:393, 1933.

124. Bulger, H. A., and Gausmann, F.: Magnesium Metabolism in Hyperparathyroidism, J. Clin. Investigation **12**:1135, 1933.

125. Caylor, H. D., and Nickel, A. C.: Multiple Myeloma Simulating Hyperparathyroidism, Ann. Surg. **97**:823, 1933.

126. Chester, W.: Multiples Myelom und Hypoproteinämie, Ztschr. f. klin. Med. **124**:466, 1933.

127. Ellermann, M., and Schrøder, G. E.: Et tilfaelde af myelom med epileptiforme kramper, Hospitalstid. **76**:102, 1933.

128. Herbert, F. K.: The Total and Diffusible Calcium of Serum and the Calcium of Cerebrospinal Fluid in Human Cases of Hypocalcemia and Hypercalcemia, Biochem. J. **27**:1978, 1933.

129. Langeron, L.; Martin, J. F., and Guichard, A.: Considerations anatomocliniques sur les myélomes multiples des os, Lyon méd. **151**:709, 1933.

130. Lenshoek, C. H.: Over stoornissen in de stoffwisseling der mineralen bij ostitis fibrosa generalisata en bij multiple myelomen, Nederl. tijdschr. v. geneesk. **77**:1193, 1933.

131. Magnus-Levy, A.: Multiple Myelome: VII. Euglobulinämie: Zur Klinik und Pathologie: Amyloidosis, Ztschr. f. klin. Med. **126**:62, 1933.

					Serum			
						Inorganic		
Year	Authors	Patient	Sex	Age, Yrs.	Calcium, Mg. per 100 Cc.	Phosphorus, Mg. per 100 Cc.	Protein, Percentage	Evidence for Diagnosis
1933	Rypins[132]	S.	F	22	11.0	4.0	....	Autopsy
1933	Wintrobe and Buell[133]	R.	F	56	"Normal"	"Normal"	....	Autopsy
1934	Albright et al.[10a]	..	F	50	"Normal"	...	....	
		M.	..	..	"Normal"	...	....	Phosphatase, 1 Bodansky unit
1934	Bodansky and Jaffe[32c]	10	M	..	....	3.1	....	Phosphatase, 4.8 Bodansky units
		11	F	60	13.2	4.0	....	Phosphatase, 1.8 Bodansky units
		12	M	40	16.1	3.4	....	Phosphatase, 4.9 Bodansky units (our case D.F.)
1934	Denker and Brock[134]	L.	F	15	9.2-9.8	3.2	4.2-5.5	"Phosphatase increased;" biopsy
1934	Ehrström[135]	J.	F	43	10.6-9.2	...	....	Biopsy
1934	dalla Volta[136]	C.	F	56	15.6-16.0	...	....	Autopsy
1935	Cantarow[137]	P.	F	41	12.9-9.2	5.8-6.8	8.7-11.3	Autopsy
1935	Berglund, Medes et al.[138]	K.	..	..	13.0	...	7.0	Bence-Jones protein
		H.	..	..	13.6	...	17.6	Bence-Jones protein
1935	Case records of Mass. Gen. Hosp. Case 21,082	..	M	50	13.9	4.7	13.5-11.7	Autopsy; phosphatase, 3.4 units (Bodansky ?)
	Case 21,052[139]	..	F	60	11.8-12.9	4.7-8.8	....	Autopsy
1935	Robbins and Kydd[96]	B.	M	60	18.1-11.3	5.5-2.3	13.1-9.8	Autopsy
		C.	M	52	11.3-10.5	9.7-4.7	6.8-6.0	Biopsy
		A.	M	34	18.8-10.3	6.6-3.1	7.8-6.4	Autopsy

NEOPLASTIC DISEASE OF THE BONES

The results of analyses of the blood in 39 cases of carcinoma with metastases to the bones and in 6 cases of primary sarcoma of the bone are summarized in the following tabulation. We have included only cases in which advanced lesions of the bone were unequivocably demonstrable by roentgenogram, and in which jaundice was not apparent clinically or on examination of the serum. The protein content of the

132. Rypins, E. L.: An Unusual Roentgenologic Finding in Multiple Myeloma, Am. J. Roentgenol. **30**:56, 1933.

133. Wintrobe, M. M., and Buell, M. V.: Hyperproteinemia Associated with Multiple Myeloma, Bull. Johns Hopkins Hosp. **52**:156, 1933.

134. Denker, P. G., and Brock, S.: The Generalized and Vertebral Forms of Myeloma: Their Cerebral and Spinal Complications, Brain **57**:291, 1934.

135. Ehrström, M. C.: Eine Studie über die Bedeutung von Totalserumkalziumanalysen in der Klinik, Acta med. Scandinav., supp. 58, 1934, p. 1.

136. dalla Volta, A.: L'iperglobulinemia quale varietà biologica dell'alterato ricambio proteico del mieloma, Arch. di pat. e clin. med. **14**:182, 1934.

137. Cantarow, A.: Bence-Jones Proteinemia in Multiple Myeloma, Am. J. M. Sc. **189**:425, 1935.

138. Berglund, H.; Medes, G.; Huber, G. C.; Longcope, W. T., and Richards, A. N.: The Kidney in Health and Disease, Philadelphia, Lea & Febiger, 1935, p. 534.

139. Case Records of the Massachusetts General Hospital, New England J. Med. **212**:204 and 353, 1935.

serum was determined when indicated, but as the values were all within normal limits, they are omitted here.

No.	Patient	Sex	Age, Yrs.	Serum: Calcium, Mg. per 100 Cc.	Serum: Inorganic Phosphorus, Mg. per 100 Cc.	Serum: Phosphatase, Bodansky Units per 100 Cc.	Serum: Nonprotein Nitrogen, Mg. per 100 Cc.	Site: Primary Neoplasm	Site: Metastases in Bones
	I. Cases of Metastatic Neoplasm of the Bone								
	Group 1: Osteolytic Metastases								
1	N. D.	F	54	10.4	5.0	11.9	36	Breast	Skull, spine, pelvis, femurs, ribs, tibia, fibula, scapula, tarsus, carpus
2	A. G.	F	42	10.2	3.9	....	..	Breast	Skull, pelvis, scapulas, spine, ribs
3	E. J.	F	35	12.3	3.1	14.8	48	Breast	Skull, spine, pelvis, ribs
4	P. G.	F	56	11.3	3.8	7.7	35	Breast	Skull, femurs, sacrum, pelvis
5	M. N.	F	63	9.9	4.3	3.4	35	Breast	Pelvis, femurs, "osteomalacia carcinomatosa"
6	G. S.	F	36	10.6	3.8	13.8	31	Breast	Pelvis, femur, spine, ribs
7	M. D.	F	48	13.9	4.9	5.8	41	Bronchus?	Skull, spine, femur, pelvis
8	A. V.	F	82	9.3	2.7	5.7	24	Lung	Pelvis, spine, ribs, skull
9	J. G.	M	61	10.4	3.6	5.1	..	Prostate?	Pelvis, spine, ribs
10	E. T.	F	40	11.4	3.4	6.5	31	Breast	Spine, pelvis
11	S. H.	F	62	13.4	1.9	2.7	34	Skin	Pelvis, femur
12	T. H.	F	49	10.8	3.4	3.3	27	Breast	Pelvis, femur
13	M. M.	F	50	10.2	3.3	5.0	29	Breast	Pelvis, femur
14	B. R.	F	59	9.9	2.8	3.4	31	Ovary	Pelvis, femur
15	J. T.	F	38	10.4	4.2	5.5	26	?	Spine, pelvis
16	M. L.	F	41	9.5	2.7	3.8	35	?	Spine, pelvis
17	J. C.	F	..	10.4	2.5	3.6	26	Breast	Spine, pelvis
18	A. M.	F	29	10.0	3.6	1.4	39	Uterus	Scapula, pelvis
19	A. F.	M	58	9.8	3.3	5.9	32	Bronchus	Ribs
20	H. Z.	F	74	9.1	3.2	2.6	31	Stomach	Femur
	Group 2: Osteolytic and Osteoplastic Metastases								
21	B. H.	F	41	13.1	2.9	6.4	34	Breast	Skull, pelvis, spine, ribs, scapula, humeri
22	F. R.	M	65	10.2	3.5	8.1	28	?	Pelvis, femurs, spine, scapulas, humeri, skull
23	E. D.	F	52	10.6	3.9	10.3	..	Breast	Pelvis, spine, femur, skull, ribs
24	M.	M	..	9.6	3.0	29.2	35	Prostate	Pelvis, spine
25	L. F.	M	68	10.0	3.1	2.9	47	Hypernephroma (?)	Spine, pelvis, skull
26	L. S.	M	58	9.1	3.2	7.6	22	Prostate	Pelvis, femur, sacrum
27	J. M.	M	54	10.3	3.1	6.4	25	?	Scapula, pelvis, spine
28	O. S.	F	38	10.8	4.1	37.7	28	Breast	Spine, pelvis, femurs
29	C. C.	F	65	9.5	3.2	13.2	36	Thyroid	Skull
	Group 3: Osteoplastic Metastases								
30	W. G.	M	74	8.0	1.8	113.5	32	Prostate	Spine, pelvis, ribs, skull, clavicles, femurs
31	A. B.	F	55	10.6	3.7	120.4	30	?	Pelvis, spine, humeri, clavicles, scapulas, skull, femurs
32	W. M.	M	66	10.6	3.1	20.2	38	Prostate	Spine, pelvis, femur
33	W. M.	M	42	9.5	4.2	20.1	57	Bladder	Spine, ribs, pelvis
34	S. H.	M	64	9.2	2.0	16.0	35	Prostate	Pelvis, spine, ribs, scapula, humerus
35	D. D.	M	58	9.5	3.6	14.0	33	Prostate	Pelvis, spine, femurs
36	P. P.	M	70	10.7	2.9	3.9	31	Prostate ?	Pelvis, femur
37	G. B.	M	66	9.9	3.9	3.7	25	?	Pelvis (Paget's disease ?)
38	H. S.	F	72	9.6	3.3	3.2	25	?	Pelvis, femur (Paget's disease ?)
39	E. K.	M	69	9.8	3.6	4.5	29	Kidney?	Pelvis
	II. Cases of Primary Neoplasm of the Bone								
40	C. P.	F	31	10.0	4.1	4.3	35	Osteoblastic type of osteogenic sarcoma, lumbar vertebra	
41	M. S.	M	16	11.0	4.2	5.0	24	Osteoblastic type of osteogenic sarcoma, jaw	
42	J. A.	M	7	9.6	2.8	6.9	20	Osteoblastic type of osteogenic sarcoma, femur; amputation; metastases to lungs	
43	H. L.	F	10	9.6	3.5	5.6	20	Osteolytic type of osteogenic sarcoma, tibia	
44	S. G.	F	42	10.9	4.2	3.4	37	Osteolytic type of osteogenic sarcoma, humerus	
45	F. P.	M	10	10.3	3.3	5.8	27	Ewing's (?) sarcoma, lumbar vertebra	

The cases of metastatic carcinoma are divided arbitrarily into 3 groups, those in each group being arranged as far as possible according to the extensiveness of the skeletal metastases. Group 1 includes cases in which the metastases appeared roentgenographically to be entirely destructive of bone.[140, 141] Group 2 includes the cases in which both destruction and proliferative reaction of bone were obvious by roentgenographic examination. Group 3 includes the cases in which the metastases appeared roentgenographically to be entirely osteoplastic. In cases 1, 3, 4, 9, 17, 24 and 27 the patients were extremely cachectic and in some instances, moribund. This may account for the low normal values for the calcium content of the serum,[142] and the low inorganic phosphorus content [143] noted for several patients. In cases 1, 3, 4, 5, 8, 9, 17, 19, 24, 26 and 27 the spread of the metastases was rapid. These three distinctions appear to be more significant with respect to variations in the constituents of the blood than the age of the patient, the duration of the disease, the localization of metastases, etc. The number of variables in this group of patients is so large, however, that no wholly satisfactory correlation with the type of metastases, the cachexia of the patient or the rate of involvement of the bone could be established.

It would appear that elevations of the calcium content of the serum occur occasionally in cases of metastatic carcinoma of the bone. Values higher than 11 mg. per hundred cubic centimeters were noted in 6 cases, in 4 instances exceeding 12 mg. When hypercalcemia occurred, it was observed only in the presence of osteolytic metastases, chiefly when these were advanced and rapidly progressive. On the other hand, in cases 1 and 2, in which the most widespread osteolytic metastases were observed, an increase in the calcium content of the serum was not found on repeated examination. With few exceptions, the inorganic phosphorus content of the serum varied within normal limits. Values as low as 1.8, 1.9 and 2 mg. per hundred cubic centimeters were observed in cachectic patients.

Extreme variations in serum phosphatase activity were observed in this group. In 12 cases the values were within the normal range. In 26 cases increases to 120.4 Bodansky units were noted. At least two

140. Histologic study, however, almost invariably reveals evidence of some proliferation of the bone in such cases.[141]

141. Willis, R. A.: The Spread of Tumours in the Human Body, London, J. & A. Churchill, Ltd., 1934, p. 335.

142. Jackson, H., Jr., and Taylor, F. H. L.: Calcium, Potassium and Inorganic Phosphate Content of the Serum in Cancer Patients, Am. J. Cancer **19**:379, 1933.

143. Youngburg, G. E., and Youngburg, M. V.: Phosphorus Metabolism: Distribution of Phosphorus in Normal and Cancer Bloods, J. Lab. & Clin. Med. **16**:253, 1930.

factors appear to be significant with respect to the level of the phosphatase activity of the blood in cases of carcinoma with metastases to the bones:

1. The serum phosphatase activity may be greatly increased in the presence of widespread, actively progressive osteoplastic metastases and may reach levels as high as any seen in cases of advanced stages of Paget's disease (cases 30 and 31).

An Irishman (case 30), aged 74, a patient of Dr. S. A. Beisler, underwent removal of a carcinoma of the prostate in 1930, the diagnosis being verified by histologic examination. Roentgenograms at that time showed no evidence of metastases to the bones or of Paget's disease. Metastases in the bones were first observed in 1932, with progressive and extensive involvement of the skeleton until the time of the patient's death in August 1934. Permission for autopsy was not obtained. We do not believe that the high values for phosphatase can be attributed to complicating Paget disease, for which there was no evidence. Whether metastases to the liver, not obvious clinically, contributed to the high values of phosphatase is not known. The bilirubin content of the serum was normal.

2. The serum phosphatase activity may be increased in cases of carcinoma with metastases to the liver, with or without jaundice. That the phosphatase activity of the blood is increased in patients with jaundice is recognized.[144] Roberts and Bodansky and Jaffe pointed out that the increase in phosphatase activity does not always parallel the degree of hyperbilirubinemia. We have observed increased serum phosphatase activity in cases of carcinoma in which jaundice was not present, the liver was not grossly enlarged or irregular and the bilirubin content of the serum was not elevated. In 6 such instances the presence of metastases in the liver, suggested only by the increase in phosphatase activity, was confirmed by exploratory celiotomy. One cannot always be certain, therefore, that the increased serum phosphatase activity found in many cases of carcinoma with metastases to the bone is not due in part to metastases in the liver which cannot be demonstrated clinically or by various laboratory procedures. We might add that in 4 cases in our series in which no clinical or chemical evidence of involvement of the liver was obtained and in which the serum phosphatase activity was within normal limits, definite hepatic metastases were noted at operation or at autopsy.

The phosphatase activity of the serum may be definitely increased in cases of carcinoma with osteolytic metastases to the bones, the values in 2 of our cases exceeding 12 Bodansky units per hundred cubic centi-

144. Roberts, W. M.: Blood Phosphatase and van den Bergh Reaction in the Differentiation of the Several Types of Jaundice, Brit. M. J. **1**:734, 1933. Bodansky, A., and Jaffe, H. L.: Phosphatase Studies: IV. Serum Phosphatase of Non-Osseous Origin: Significance of the Variations of Serum Phosphatase in Jaundice, Proc. Soc. Exper. Biol. & Med. **31**:107, 1933.

meters. In 16 of the 19 cases in this series, however, the values obtained were less than 8 Bodansky units.

Extensive studies of variations in the calcium content of the serum (reviewed by Jackson and Taylor [142]) and in the amount of inorganic phosphorus [143] in cases of neoplastic disease have appeared in the literature. These show either normal or moderately lowered values. Comparatively few observations have been made on the amount of serum calcium and inorganic phosphorus or on phosphatase activity in cases of carcinoma with extensive metastases to the bone. The available data have been summarized. Most of the authors cited have not distinguished between predominantly osteolytic and predominantly osteoplastic metastases in the bone; so we are unable to say whether the apparent differences demonstrated in our analyses explain in part the variable results recorded in the following tabulation.

					Blood				
Year	Author	Case	Sex	Age, Yrs.	Calcium, Mg. per 100 Cc.	Inorganic Phosphorus, Mg. per 100 Cc.	Phosphatase, Units per 100 Cc.	Primary Neoplasm	Comment
1925	Andersen[145]	H.	F	48	16.7-21.8	.....	....	Breast	Metastases to femurs
1929	Kay[26]	..	..	..	.....	.....	>1.3	?	Advanced metastases to spine and pelvis,
1930	Alwens[146]	..	..	..	"Up to 16.8%"	.....	....	?	"In occasional cases with osteoclastic metastases"
1930	Kay[147]	..	F	41	.....	.....	0.44	?	Metastases to spine
			F	56	.....	.....	0.74	?	Metastases to spine and pelvis
			F	50	.....	.....	0.25	?	Metastases to pelvis
			M	16	.....	.....	0.24	Femur	Periosteal sarcoma
			F	17	.....	.....	0.63	Femur	Sarcoma
1931	Brull et al.[148]	F.	F	52	11.6-12.9	5.6	....	Breast	Extensive metastases to bone
1931	Jores[111]	..	..	..	.....	.....	....	.....	"Occasional hypercalcemia in osteoclastic metastases"
1931	Mason and Warren[89]	..	F	47	12.9-17.6	2.5-4.5	....	Breast	Extensive metastases to bone
1932	Aub and Farquharson[115]	M.	F	47	10.7-10.5	5.1-3.9	....	Breast	Extensive metastases to bone
		N.	F	33	9.3	3.6	....	Breast	Extensive metastases to bone
1932	Martin and Sarasin[74]	..	M	..	10.6-11.6	3.9	....	Prostate	Metastases to bone

145. Andersen, W. T.: Some Researches on Calcium Content of Serum, Hospitalstid. **68**:1177, 1925.

146. Alwens, W.: Knochenerkrankungen in ihren Beziehungen zum Kalkstoffwechsel, zur inneren Sekretion und zu den Vitaminen: Klinik und Therapie vom Standpunkt des Internisten, Verhandl. d. Gesellsch. f. Verdauungs- u. Stoffwechselkr. **10**:170, 1930.

147. Kay, H. D.: Plasma Phosphatase: II. The Enzyme in Disease, Particularly in Bone Disease, J. Biol. Chem. **89**:249, 1930.

148. Brull, L.; Poverman, R., and Garin, M.: Contributions à l'étude du métabolisme calcique: Ostéoporose généralisée dans un cas de carcinomatose métastique avec fractures spontanées multiples, Rev. belge sc. méd. **3**:977, 1931.

Year	Author	Case	Sex	Age, Yrs.	Blood: Calcium, Mg. per 100 Cc.	Blood: Inorganic Phosphorus, Mg. per 100 Cc.	Blood: Phosphatase, Units per 100 Cc.	Primary Neoplasm	Comment
1932	Race[149]	..	..	..	.....	.....	1.56	?	Four cases of secondary carcinomatosis of bone
		..	..	..	.....	.....	1.50	?	
		..	..	..	.....	.....	0.45	?	
		..	..	..	.....	.....	0.18	?	
1932	Solcard et al.[150]	P.	F	44	27.2 (whole blood)	.....	....	Breast	Metastases to bone
1933	Brunschwig[151]	P.	F	44	10.5	4.2	....	Breast	Metastases to bone
1933	Bulger and Gausmann[124]	22,810	..	..	14.9-15.1	2.5-2.7	....	Hypernephroma	Metastases to bone
1933	Centeno and Masciocchi[152]	L.	F	40	12.0	.....	....	Breast	Extensive metastases to bone
1933	Hoffmeister[153]	..	..	..	"Normal"	.....	....	Prostate	Osteoclastic metastases, 4 cases
1933	Jackson and Taylor[142]	..	M	72	9.7	.....	....	Prostate	Metastases to scapula and clavicle
		..	..	79	8.0	.....	....	Buccal mucosa	Extension to bone
		..	..	60	7.6	.....	....	Jaw	Invasion of bone
		..	M	72	7.2	.....	....	Prostate	Extensive metastases to bone
		..	..	53	7.2	.....	....	Skin	Involvement of bone
1933	Mocquot et al.[154]	E.	F	39	11.5-15.2	.....	....	Breast	Extensive metastases to bone
1934	Bodansky and Jaffe[32c]	..	M	42	10.5	6.0	28.1	?	Metastases to bone
		..	F	38	.....	5.5	9.4	?	Metastases to spine, pelvis and rib
		..	F	37	9.8	4.9	56-85	Bronchus	Extensive sclerosing metastases to skeleton
1934	Ehrström[125]	T.	M	67	7.0-9.0	.....	....	Prostate	Pelvis
1935	Robbins and Kydd[96]	..	..	..	18.5-11.6	.....	....	?	Hypercalcemia in 5 cases with metastases to bone

Data on 6 cases of primary sarcoma of the bone are included in the summary on p. 403. The serum phosphatase activity was essentially normal for persons of the ages of the respective patients in this series. Kay [26] found the plasma phosphatase activity to be 0.63 Kay units in a case of sarcoma of the femur. Jenner and Kay [27] reported a value of 11.5 Jenner and Kay units in a case of osteogenic sarcoma. Bodansky and Jaffe [32c] made examinations in 5 cases of osteogenic sarcoma. The

149. Race, J.: The Phosphatase Test in the Arthritides and Osteitides, Arch. M. Hydrol. **10**:6, 1932.

150. Solcard; Rolland, and Quérangel des Essarts, J.: Carcinomatose osseuse généralisée consécutive a un cancer du sein, Ann. d'anat. Path. **9**:552, 1932.

151. Brunschwig, A.: Conversion of Osteolytic Carcinoma Metastases to Bone into Osteoblastic Ones by Large Doses of Calcium, Proc. Soc. Exper. Biol. & Med. **30**:1293, 1933.

152. Centeno, A. M., and Masciocchi, A.: Cáncer del seno y metástasis óseas, Rev. Asoc. méd. argent. **47**:2545, 1933.

153. Hoffmeister, W.: Blutkalkspiegel bei Knochenbrüchen und-erkrankungen, Deutsche Ztschr. f. Chir. **240**:414, 1933.

154. Mocquot, P.; Herrenschmidt, A., and Worms, R.: Métastases diffuses du squelette chez des malades atteintes de cancer du sein, Bull. Assoc. franç. p. l'étude du cancer **22**:526, 1933.

serum phosphatase activity varied from 3 to 16.6 Bodansky units. In 2 cases of Ewing's tumor the values were within the range observed for normal children. Franseen and Aub [155] reported increased values for plasma phosphatase in cases of osteogenic sarcoma. They expressed the belief that the determination of blood phosphatase may be useful in the early diagnosis of osteogenic sarcoma and in the detection of metastases.

COMMENT

The data summarized in the preceding pages permit certain inferences regarding the value and limitations of the determination of serum calcium, inorganic phosphorus and phosphatase activity in the differential diagnosis of the diseases of bone under consideration:

1. *Hyperparathyroidism.*—When hypercalcemia, hypophosphatemia and increased blood phosphatase activity coexist, as in cases of uncomplicated classic hyperparathyroidism, confusion is unlikely. We have encountered similar findings only in an occasional case of carcinoma with advanced skeletal metastases in which the hypercalcemia was related, presumably, to neoplastic destruction of the bone, the hypophosphatemia, probably, to cachexia, and the increased blood phosphatase to involvement of the bone or liver. Difficulties in interpretation are due more frequently, in about one fifth of the cases of hyperparathyroidism, to the absence of consistent elevation of the calcium content of the serum above 12 mg. per hundred cubic centimeters; they were due to the lack of consistent hypophosphatemia in approximately one half of the cases reported. Hypercalcemia is observed in many cases of multiple myeloma, in occasional cases in which extensive osteolytic carcinomatous metastases are present and, rarely, in other conditions [156] (case of E. M.). Hypophosphatemia occurs also in cases of osteomalacia and rickets. Increased blood phosphatase activity within the range observed in hyperparathyroidism may be encountered in cases of Paget's disease, rickets, osteomalacia, carcinoma with metastases to the bone and obstructive jaundice. It is apparent, therefore, as several observers have pointed out,[157] that while studies of the blood may be of great value in confirming or excluding the diagnosis of hyperparathyroidism, interpre-

155. Franseen, C. C., and Aub, J. C.: Phosphatase Content of the Blood Plasma and Tumor Tissue in Malignant Diseases of Bone, J. Clin. Investigation **13**:698, 1934.

156. Rogoff, J. M., and Stewart, G. N.: Further Blood Studies (Cholesterol and Calcium) in Control Adrenalectomized Dogs, Am. J. Physiol. **86**:25, 1928. Benedict, E. M., and Turner, K. B.: The Serum Calcium in Polycythemia Vera, J. Clin. Investigation **9**:263, 1930.

157. Gutman, Swenson and Parsons.[8] Albright, Aub and Bauer.[10a] Robbins and Kydd.[96] Jores.[111]

tation of their significance without careful consideration of the clinical and roentgenologic aspects of the case may lead to grave error.

2. Paget's Disease.—It is an extraordinary fact that, in spite of the extensive skeletal changes which may take place in this disease, the content of calcium and inorganic phosphorus of the serum remains within normal limits. In this respect, as in many other clinical, pathologic and metabolic features,[158] hyperparathyroidism and Paget's disease differ so widely that it seems improbable that they could be different phases of the same disease, as some authors maintain. The finding of hypercalcemia in a case ostensibly one of Paget's disease should lead to a review of the evidence, since the literature contains several proved cases of hyperparathyroidism presenting roentgenologic features ascribed to Paget's disease.[10] As the only recognized abnormality of the blood in Paget's disease, the increase in phosphatase activity, first noted by Kay,[26] is of special interest. An unequivocal increase in blood phosphatase activity is demonstrable in almost all cases of polyostotic Paget's disease, in advanced stages of the disease reaching levels forty or more times the mean normal value. Successive determinations indicate that the level of serum phosphatase activity in most cases of Paget's disease remains remarkably constant for years.[159]

The degree of elevation of blood phosphatase activity varies widely for different patients with osteitis deformans. Kay[147] and others[160] have suggested that a rough proportionality exists between the extensiveness of the involvement of bone and the level of phosphatase activity, an observation corroborated by the distribution of values for serum phosphatase in the several groups of cases in our series (summary of cases of Paget's disease, p. 389. There are discrepancies in this relation, however (group 2 in the summary just mentioned), which have led to the suspicion that the activity of the osseous lesions may be another factor affecting the level for blood phosphatase in Paget's disease.[160] In some of our patients with unexpectedly high (or low) levels for serum phosphatase as compared with the extent of involvement of the bones revealed by roentgenograms, subsequent roentgenographic and clinical studies did, in fact, suggest unusually rapid (or slow) development of the disease.[5c] The determination of serum phosphatase may, therefore, prove to be of value in prognosis. We were unable to note any convincing correlation between the stage of the lesions in cases of Paget's disease or the localization of the process and

158. Bauer, W.: Hyperparathyroidism: A Distinct Disease Entity, J. Bone & Joint Surg. **15**:135, 1933.

159. Gutman, A. B., and Gutman, E. B.: Paget's Disease: Relative Constancy of Serum Phosphatase Levels over Periods up to Two Years, Proc. Soc. Exper. Biol. & Med. **33**:150, 1935.

160. Bodansky and Jaffe.[32c] O'Reilly and Race.[5b]

the level for serum phosphatase. It was noted, however, as indicated in the summary of cases, that extensive involvement of the skull was almost invariably associated with relatively high values.

Since even widespread involvement by Paget's disease may be present without eliciting clinical symptoms or signs, the determination of serum phosphatase provides a useful means of corroborating the diagnosis as made by appropriate roentgenographic examination. However, the determination, in our experience, has been of little value in the diagnosis of early, localized Paget's disease, as the increase in serum phosphatase activity in such cases is likely to be unimpressive, and may be absent. In cases of more advanced disease the roentgenographic diagnosis is usually obvious, except in respect to differentiation from osteoplastic metastases in the bones. But in the latter condition, as has already been indicated, particularly in cases of carcinoma of the prostate, the serum phosphatase activity may also be markedly increased. Other diseases in which high levels for blood phosphatase are encountered have already been enumerated. The data at hand are in accord with Kay's conclusion [82a] that the increased blood phosphatase activity in cases of osteitis deformans is not specific and is probably a result rather than the cause of the disease.

3. *Multiple Myeloma.*—The presence of hyperproteinemia [102] and hypercalcemia [98] or of either alone may provide valuable support for the diagnosis of multiple myeloma. These abnormalities are not demonstrable in many cases, however (table 3 and the summary of reports on multiple myeloma, p. 399), and when found they may disappear at irregular intervals or for long periods while the patient is under observation. In cases of diffuse involvement of the skeleton certain roentgenographic features of hyperparathyroidism may be simulated, and this fact and the frequent occurrence of hypercalcemia together with the rare observation of an equivocal enlargement of the parathyroid glands have led some investigators to postulate an associated state of "secondary hyperparathyroidism," as already mentioned. The inorganic phosphorus content of the serum is within normal limits except when renal insufficiency causes retention of phosphates. The serum phosphatase activity in cases of multiple myeloma, in contradistinction to that in cases of classic hyperparathyroidism, is usually essentially normal or only slightly elevated. Rowntree, however, stated that he encountered increased values in several cases.[161] The finding of Bence-Jones bodies in the urine is of value in differentiating multiple myeloma and hyperparathyroidism, since, with the possible exception of a single instance, Bence-Jones proteinuria has not been observed in cases of hyperparathyroidism.

161. Rowntree, L. G.: Progress Relative to Diseases of the Ductless Glands, Pennsylvania M. J. **36**:646, 1933.

4. *Metastatic Carcinoma of the Bone.*—The occasional occurrence of hypercalcemia in cases of extensive osteolytic metastases in the bones may lead to confusion with hyperparathyroidism or multiple myeloma. Similarly, the increased serum phosphatase activity observed particularly in association with diffuse osteoplastic metastases in the bones may be confused with that found in cases of Paget's disease.

With regard to the physiologic significance of increased blood phosphatase activity, the fundamental work of Robison and his associates [162] led him to suggest that it is the result of an increase in specific cellular activities leading to formation of bone.[163] The data assembled in this study, apart from those concerned with conditions in which the increase is apparently of nonosseous origin,[164] are compatible with this view. The high values for blood phosphatase in Paget's disease [26] and in association with diffuse osteoplastic metastases in the bones are explained satisfactorily by this mechanism. In rickets, although excessive formation of bone does not occur, there is marked proliferation of cartilage cells, a fertile source of phosphatase, as Robison and Soames [165] have shown. The increased blood phosphatase activity in hyperparathyroidism, in which dissolution of bone is the most striking feature, would appear at first sight to be inconsistent with the conception that blood phosphatase is related to formation of bone. Histologic studies,[166] however, reveal extensive repair of bone concomitant with destruction, and the increase in blood phosphatase activity may be the result of such formation of new bone. This would explain why the level for blood phosphatase remains elevated so long and why it may even rise temporarily (case 1) after ablation of the parathyroid tumor. Albright, Aub and Bauer [10] have observed a rough correlation between the level of phosphatase in the plasma and the number of osteoblasts in sections of bone taken for biopsy after operation. A fair degree of correlation between the rate of redeposition of bone observed roentgenographically and the level for serum phosphatase was noted after operation in case 1 of our series. Whether the moderate increase in serum phosphatase activity

162. Robison, R.: The Possible Significance of Hexosephosphoric Esters in Ossification, Biochem. J. **17**:286, 1923.

163. Robison, R.: The Significance of Phosphoric Esters in Metabolism, New York, New York University Press, 1932.

164. Bodansky, A.: Phosphatase Studies: VI. Non-Osseous Origins of Serum Phosphatase: Its Increase After Ingestion of Carbohydrates, J. Biol. Chem. **104**: 473, 1934.

165. Robison, R., and Soames, K. M.: The Possible Significance of Hexosephosphoric Esters in Ossification: II. The Phosphoric Esterase of Ossifying Cartilage, Biochem. J. **18**:740, 1924.

166. Schmorl, G.: Zur Technik der Knochenuntersuchung: Bemerkungen zur Diagnose der Ostitis deformans Paget, Ostitis fibrosa v. Recklinghausen und Osteoporose, Beitr. z. path. Anat. u. z. allg. Path. **87**:585, 1931.

found in many cases of carcinoma with predominantly osteolytic metastases in the bones is due in part to a proliferative reaction of the bone not apparent in roentgenograms is an interesting speculation. In multiple myeloma, in which, it is said, proliferative reaction of bone is virtually absent, the increase in serum phosphatase activity is slight or absent, despite extensive involvement of the bone.

SUMMARY

The calcium and inorganic phosphorus content of the serum and the serum phosphatase activity were determined in 4 cases of hyperparathyroidism, 76 cases of Paget's disease, 6 cases of multiple myeloma and 45 cases of neoplastic disease of the bones. The relevant data from the literature are summarized. The usefulness and limitations of these determinations in the differential diagnosis of the diseases of bone under consideration are discussed.

1. Of the cases of hyperparathyroidism in which determinations are recorded in the literature, about four fifths showed consistent hypercalcemia, with a calcium content of more than 12 mg. per hundred cubic centimeters, and about one half, consistent hypophosphatemia, with an inorganic phosphorus content of less than 2.5 mg. Increase in blood phosphatase activity was found in every case of classic hyperparathyroidism with definite changes in the bones in which determinations were made (28 cases). Complicating factors affecting these values and their significance in differential diagnosis are discussed. The question of "secondary" hyperparathyroidism is considered.

2. The calcium and inorganic phosphorus contents of the serum are within normal limits in cases of uncomplicated Paget's disease. The serum phosphatase activity is almost invariably increased in cases of advanced disease reaching values forty or more times the mean normal value. The level for serum phosphatase is roughly proportional to the extent of involvement of the bones and is probably affected also by the activity of the osseous lesions. In this sense, the determination may be of value in prognosis. Increased blood phosphatase activity is not specific for Paget's disease. The increase in instances of early, localized Paget's disease is often equivocal, so that the determination is of little value in such cases. Nor is it usually of assistance in differentiating cases of osteoplastic metastases in the bone, in which serum phosphatase activity is also increased.

3. Definite hypercalcemia has been observed in a number of cases of multiple myeloma. The inorganic phosphorus content of the serum is normal or somewhat elevated. The serum phosphatase activity is usually normal or slightly elevated.

4. Hypercalcemia is present in occasional cases of carcinoma with extensive, predominantly osteolytic metastases to the bones. The amount of inorganic phosphorus in the serum is usually within normal limits, but it may be depressed in cases of advanced cachexia or increased when renal insufficiency is present. The serum phosphatase activity is usually moderately increased or essentially normal.

In cases of carcinoma with extensive, predominantly osteoplastic metastases, the serum phosphatase activity may be as high as that in advanced Paget's disease. The content of calcium and that of inorganic phosphorus in the serum are normal, except when renal insufficiency is present. In cases of carcinoma with metastases to the liver, with or without jaundice, variable increases in serum phosphatase activity are observed.

5. The physiologic significance of increased serum phosphatase activity in cases of disease of the bone is discussed.

NEUROPATHY IN DIABETES

LIPID CONSTITUENTS OF THE NERVES CORRELATED WITH THE CLINICAL DATA

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Contact with many persons with diabetes impresses one with the frequency of neuropathy in these patients. A study of this neuropathy from any approach is likely to be interesting and helpful in the present state of knowledge about it. The clinicians have noted evidence of degeneration, and the pathologists have partially confirmed their findings. We attempted to investigate this degeneration from the point of view of the fatty constituents of the nerves. The stains used by the pathologists indicated damage to the lipid sheath of the nerves but did not reveal the character of the change in detail.

In a previous paper [1] we reviewed the appropriate literature and gave a preliminary report of the results of the chemical analysis of twenty nerves of diabetic patients as compared with nerves from persons without diabetes. In the present paper are included analyses of thirty-two more nerves from diabetic patients and a comparison of the entire series of fifty-two nerves obtained from forty-seven diabetic patients with twenty-three nerves from persons without diabetes. Individual values for nerves are listed in tables 1 and 2. The average phospholipid, cholesterol and cerebroside content of nerves from diabetic patients is much less than that of normal nerves.

The diabetic patients were of the elderly, sclerotic type and suffered from diabetes of mild or moderate severity. Their condition was not primarily diabetic neuritis, although twenty of them complained of pain, paresthesia or muscular paresis. Abnormal pupillary reactions were noted in four cases. Hemiplegia had occurred in case 11106. A diagnosis of thrombosis of the femoral artery was made in cases 5423 and 10582. Syphilis was present in case 10171, but there was no serologic evidence of involvement of the nervous system. In case 3575 it was suspected that the patient had pernicious anemia, but it was not

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1. Jordan, W. R.; Randall, L. O., and Bloor, W. R.: Neuropathy in Diabetes Mellitus, Arch. Int. Med. **55**:26 (Jan.) 1935.

TABLE 1.—*Analyses of Normal Nerves*

Case No.	Nerve	Phospholipid		Cholesterol		Cerebroside		Fat, Moist Weight, per Cent	Water, per Cent	Phospholipid, Cholesterol, per Cent	Phospholipid, Cerebroside, per Cent	Cholesterol Cerebroside, per Cent
		Moist Weight, per Cent	Moist Weight, Fat-Free, per Cent	Moist Weight, per Cent	Moist Weight, Fat-Free, per Cent	Moist Weight, per Cent	Moist Weight, Fat-Free, per Cent					
7632	R. femoral.....	4.51	4.85	1.11	1.17	1.78	1.90	5.32	....	4.05	2.54	0.63
7632	L. femoral.....	4.94	5.37	1.61	1.73	1.61	1.73	7.18	....	3.06	3.06	1.00
62858	L. femoral.....	4.93	5.35	1.45	1.56	1.13	1.21	6.94	....	3.40	4.42	1.30
62858	R. femoral.....	4.44	5.05	1.32	1.44	0.70	0.77	8.25	....	3.36	6.34	1.89
46506	R. femoral.....	3.72	4.60	1.16	1.42	0.86	1.06	18.31	....	3.21	4.34	1.35
46506	L. femoral.....	4.17	5.05	1.05	1.25	1.01	1.20	16.08	....	3.99	4.13	1.04
75201	L. femoral.....	4.55	5.60	1.39	1.71	1.54	1.88	18.48	....	3.28	2.95	0.90
53033	R. femoral.....	4.80	5.04	1.48	1.54	1.63	1.70	3.81	....	3.25	2.95	0.91
62758	R. tibia.....	4.05	4.15	1.86	1.97	2.45	2.62	6.00	....	2.18	1.65	0.76
72926	L. sciatic.....	4.58	5.15	1.62	1.82	1.02	1.16	11.24	....	2.82	4.48	1.59
62428	L. femoral.....	4.22	4.60	1.35	1.45	1.10	1.18	7.18	70.0	3.12	3.84	1.23
62428	R. femoral.....	4.45	4.90	1.48	1.61	1.41	1.54	8.00	66.7	3.00	3.16	1.02
64097	L. femoral.....	4.16	4.48	1.35	1.44	2.30	2.45	6.76	70.5	3.08	1.81	0.59
64097	R. femoral.....	4.81	5.07	1.41	1.49	2.40	2.52	5.10	73.5	3.41	2.00	0.59
63216	R. femoral.....	3.76	3.93	1.06	1.11	1.76	1.84	4.04	72.3	3.55	2.14	0.60
63739	L. femoral.....	5.24	5.74	1.89	2.08	1.81	1.99	9.05	62.4	2.77	2.80	1.05
64411	L. femoral.....	5.90	6.60	1.86	2.08	2.08	2.32	10.42	62.0	3.17	2.84	0.90
A2257	R. femoral.....	5.06	5.54	1.77	1.88	2.05	2.24	8.25	61.0	2.87	2.47	0.86
53300	L. femoral.....	4.30	5.85	1.46	1.58	1.20	1.29	7.17	66.8	2.95	3.58	1.22
55894	R. femoral.....	3.26	3.55	1.19	1.30	2.75	3.00	8.00	68.4	2.74	1.18	0.43
70496	L. femoral.....	5.75	5.90	2.40	2.45	1.76	1.80	2.31	78.0	2.40	3.27	1.36
11806	Femoral.....	4.80	5.04	1.48	1.54	1.63	1.70	4.80	....	3.24	2.84	0.91
31:185	Pelvic.....	4.00	4.55	1.66	1.91	1.18	1.35	12.50	....	2.41	3.38	1.41
	Average.....	4.54	5.04	1.49	1.63	1.61	1.76	8.48	65.5	3.10	3.14	1.02

TABLE 2.—*Analyses of Nerves from Diabetic Patients*

Case No.	Nerve	Phospholipid		Cholesterol		Cerebroside		Fat, Moist Weight, per Cent	Phospholipid, Cholesterol, per Cent	Phospholipid, Cerebroside, per Cent	Cholesterol Cerebroside, per Cent
		Moist Weight, per Cent	Moist Weight, Fat-Free, per Cent	Moist Weight, per Cent	Moist Weight, Fat-Free, per Cent	Moist Weight, per Cent	Moist Weight, Fat-Free, per Cent				
1605	R. posterior tibial	1.27	1.34	0.53	0.56	1.13	1.20	5.45	2.40	1.12	0.47
2629	R. posterior tibial	0.89	1.00	0.35	0.40	0.32	0.36	10.37	2.54	2.78	1.10
2863	L. posterior tibial	1.48	1.58	0.62	0.66	1.31	1.39	6.08	2.39	1.13	0.47
3575	R. femoral	1.94	2.04	1.11	1.16	0.34	0.36	4.07	1.75	5.70	3.26
3575	L. femoral	1.59	1.65	0.54	0.56	0.63	0.65	3.20	2.95	2.52	1.17
3962	L. posterior tibial	0.92	1.09	0.35	0.42	0.44	0.52	15.30	2.63	2.09	0.80
5423	R. anterior tibial	0.90	1.30	0.33	0.48	0.54	0.78	31.20	2.72	1.67	0.61
5585	R. posterior tibial	0.47	0.50	0.28	0.29	0.64	0.68	5.55	1.68	0.74	0.44
6088	L. external peroneal	1.75	2.62	0.53	0.79	1.05	1.56	33.60	3.30	1.67	0.50
6088	L. posterior tibial	2.18	2.54	1.19	1.37	1.18	1.37	13.70	1.83	1.85	1.01
6115	L. femoral	3.57	4.01	1.33	1.50	0.84	0.94	11.00	2.69	4.25	1.58
6162	R. femoral	2.24	2.50	0.79	0.88	1.83	2.06	11.10	2.84	1.23	0.43
6177	R. posterior tibial	1.62	1.77	0.56	0.62	0.74	0.82	9.41	2.90	2.19	0.76
7052	R. posterior tibial	1.44	1.63	0.56	0.64	0.88	1.00	11.45	2.57	1.64	0.64
7465	L. posterior tibial	0.52	0.54	0.23	0.24	0.50	0.52	4.15	2.26	1.04	0.46
7575	L. posterior tibial	1.49	1.81	0.38	0.46	0.76	0.92	17.60	3.92	1.96	0.50
9191	L. femoral	3.71	5.12	1.08	1.56	0.82	1.19	30.08	3.44	4.30	1.32
9429	L. posterior tibial	1.30	1.35	0.48	0.50	0.83	0.85	2.60	2.70	1.57	0.58
9827	L. femoral	3.85	7.15	1.15	1.62	1.60	2.97	40.00	3.35	2.41	0.72
9931	R. posterior tibial	1.27	1.46	0.33	0.38	0.66	0.76	13.40	3.84	1.93	0.50
10092	L. sciatic (thigh)	1.27	1.38	0.54	0.59	1.07	1.16	8.65	2.35	1.19	0.50
10097	R. posterior tibial	1.16	1.33	0.48	0.55	0.77	0.87	11.80	2.42	1.51	0.62
10171	L. posterior tibial	1.27	1.38	0.55	0.60	0.98	1.07	8.30	2.31	1.30	0.56
10205	L. sciatic (thigh)	1.40	1.62	0.76	0.88	1.07	1.23	13.80	1.84	1.31	0.71
10205	L. peroneal	0.87	1.00	0.39	0.44	0.64	0.72	11.15	2.23	1.36	0.61
10207	R. posterior tibial	0.31	0.38	0.19	0.24	0.36	0.45	19.00	1.63	0.86	0.53
10582	L. posterior tibial	0.94	1.13	0.32	0.38	0.27	0.32	16.45	2.94	3.48	1.18
10677	L. posterior tibial	0.48	0.54	0.21	0.24	0.41	0.46	11.10	2.28	1.17	0.51
10712	R. sciatic	3.38	3.87	1.20	1.37	0.91	1.03	12.65	2.82	3.72	1.32
10712	L. sciatic	2.55	3.02	0.94	1.11	1.13	1.34	15.60	2.71	2.26	0.83
10723	R. posterior tibial	1.10	1.20	0.40	0.44	0.49	0.53	8.55	2.75	2.24	0.82
10760	R. posterior tibial	0.78	0.94	0.28	0.34	0.45	0.54	17.50	2.78	1.74	0.62
10791	R. posterior tibial	0.83	0.93	0.23	0.26	0.95	1.09	12.90	3.46	0.88	0.24
10799	R. posterior tibial	1.06	1.16	0.42	0.47	1.00	1.12	10.50	2.45	1.03	0.42
10803	L. posterior tibial	0.73	0.83	0.16	0.18	0.13	0.15	33.45	4.45	5.60	0.81
10804	R. femoral	3.94	4.58	1.22	1.42	1.13	1.33	14.65	3.22	3.48	1.08
10964	R. posterior tibial	1.60	3.64	0.54	1.38	0.63	1.40	56.37	2.96	2.54	0.85
10974	L. posterior tibial	1.22	1.30	0.48	0.50	0.76	0.79	4.95	2.54	1.60	0.63
11005	R. posterior tibial	1.20	1.31	0.48	0.54	0.28	0.32	11.86	2.50	4.30	1.71
11079	L. posterior tibial	0.76	0.85	0.30	0.34	0.50	0.56	10.70	2.53	1.52	0.60
11080	R. posterior tibial	1.48	1.62	0.53	0.56	0.52	0.54	8.18	2.80	2.80	1.02
11082	R. femoral	3.16	3.60	0.89	1.03	1.85	2.13	12.95	3.55	1.71	0.48
11082	R. sciatic	2.10	2.32	0.87	0.96	0.68	0.74	8.42	2.42	3.09	1.28
11088	L. posterior tibial	0.98	1.03	0.51	0.53	1.40	1.49	4.45	1.92	0.70	0.37
11106	L. posterior tibial	0.65	0.80	0.22	0.27	0.61	0.78	18.48	2.95	1.07	0.36
11108	R. posterior tibial	1.10	1.63	0.45	0.53	1.46	1.70	14.10	2.45	0.75	0.31
11128	R. posterior tibial	1.50	1.66	0.66	0.72	0.85	0.93	8.50	2.27	1.77	0.78
11144	L. posterior tibial	1.12	1.81	0.50	0.54	0.83	1.11	7.35	2.24	1.35	0.60
11147	Pelvic	1.80	2.06	0.63	0.73	0.76	0.88	13.05	2.86	2.37	0.83
Path. No.											
14671	L. posterior tibial	1.33	1.39	0.48	0.50	0.80	0.84	4.55	2.77	1.64	0.60
16127	R. posterior tibial	0.61	0.67	0.24	0.27	1.75	1.95	9.60	2.54	0.35	0.14
12095	R. posterior tibial	0.57	0.66	0.26	0.31	0.94	1.10	14.80	2.20	0.61	0.25
	Average	1.49	1.82	0.59	0.69	0.83	0.99	13.84	2.67	2.04	0.70

proved. Alcoholism of a great degree did not occur in this series, and only three patients admitted using alcohol at all. A determination of the cholesterol content of the blood was made on nine patients, and the cholesterol level was found to be elevated only in case 6115.

In tables 3 and 4 are compared the average values [2] according to the level of the nerve examined. The increased pathologic change in the more peripheral portion of the nerve is striking. Only one nerve from below the knee contained as much as 2 per cent phospholipid, and in only two patients did the nerves at the pelvic level contain as little as 2 per cent phospholipid. This difference may vitiate to some extent the

TABLE 3.—*Comparison of Average Values with Respect to the Level of the Nerve Examined*

Level of Nerve	No. of Nerves	Phospholipid, per Cent	Cholesterol, per Cent	Cerebroside, per Cent
Pelvic	12	2.82	0.98	1.04
Thigh	2	1.34	0.65	1.07
Lower part of leg	38	1.08	0.42	0.76

TABLE 4.—*Comparison of Lipid Values at Different Levels in Case 10205*

Name of Nerve	Level	Phospholipid, per Cent	Cholesterol, per Cent	Cerebroside, per Cent
Sciatic	Thigh	1.40	0.76	1.07
Peroneal	Lower part of leg	0.87	0.39	0.64

TABLE 5.—*Comparison of the Average Values with Respect to Age* *

Age	No. of Nerves	Phospholipid, per Cent	Cholesterol, per Cent	Cerebroside, per Cent
6th decade	10	0.99	0.39	0.70
7th decade	14	1.09	0.42	0.65
8th decade	14	1.14	0.45	0.91

* Only the nerves of the lower part of the legs were studied.

results of the comparison of the nerves from persons without diabetes with the nerves from persons with diabetes, since only one of the nerves in the former group was from below the knee. The lipid content of this nerve, however, was similar to that of the nerves at the pelvic level from the same group. Furthermore, as will be seen later, a comparison of the pelvic nerves from persons without diabetes with the pelvic nerves from persons with diabetes confirms the pathologic changes exhibited by a comparison of the data in tables 1 and 2. Nevertheless, in diabetic persons the level of the nerve makes such a tremendous differ-

2. Comparison in all the tables includes only nerves from diabetic persons unless otherwise stated.

ence in the lipid values as to upset comparisons of the effect of other factors unless one utilizes nerves of a similar level. Its difference accounts for certain apparent influences reported in the former paper that seem less important now that we have enough specimens of the same level to compare. In the following comparisons are various possible influencing factors. We have indicated when only nerves of a similar level were used.

The ages of the patients ranged from 52 to 79.8 years. Our data indicate that age alone does not influence the chemical pathologic changes in the nerves of diabetic persons.

TABLE 6.—*Comparison of Average Values with Respect to Arteriosclerosis* *

Degree of Arteriosclerosis	No. of Nerves	Phospholipid, per Cent	Cholesterol, per Cent	Cerebroside, per Cent
Mild to moderate	6	3.19	1.04	1.16
Advanced	6	2.45	0.93	0.92

* Only the pelvic nerves were studied.

TABLE 7.—*Comparison of Average Values with Respect to Arteriosclerosis* *

Degree of Arteriosclerosis	No. of Nerves	Phospholipid, per Cent	Cholesterol, per Cent	Cerebroside, per Cent
Mild to Moderate	5	1.42	0.56	0.81
Advanced	33	1.03	0.40	0.75

* Only the nerves of the lower part of the legs were studied.

TABLE 8.—*Comparison of Average Values with Respect to Circulation in the Lower Part of the Legs* *

Condition of Circulation	No. of Nerves	Phospholipid, per Cent	Cholesterol, per Cent	Cerebroside, per Cent
Fair	6	1.23	0.44	0.83
Poor	32	1.05	0.42	0.65

* Only the nerves of the lower part of the legs were studied.

Contrarily, vascular disease,[3] which in persons without diabetes is evidence primarily of advancing age, appears to affect the nerves adversely. This is illustrated by a comparison of nerves from patients with different degrees of arteriosclerosis or of circulatory deficiency of the lower part of the legs. At any given level, other factors being equal, these lipid constituents of the nerve will decrease with increasing arteriosclerosis. In this series we had no diabetic patient with normal arteries and circulation. It should be well worth while to make such a

3. In case 11005 we listed the arteriosclerosis as 2+ in our previous paper. Although this was true of the patient's arteries in general, we changed it in this paper to 3+ because of advanced arteriosclerosis in the leg from which the nerve was obtained.

study of young diabetic patients and of persons without diabetes with and without vascular disease. Two of our patients without diabetes had considerable arteriosclerosis and no diminution in the lipid values. In table 9 are compared the pelvic nerves from these two patients with the pelvic nerves from our diabetic patients. These data, though meager, tend to discourage the belief that the neuropathy of diabetes is due solely to arteriosclerosis.

TABLE 9.—*Comparison of Average Values for Pelvic Nerves of Persons with Diabetes with Those of Persons Without Diabetes Who Had Arteriosclerosis*

Subjects	No. of Cases	Phospholipid, per Cent	Cholesterol, per Cent	Cerebroside, per Cent
Those without diabetes	2	4.40	1.57	1.73
Those with diabetes	12	2.82	0.98	1.04

TABLE 10.—*Comparison of Average Values with Respect to the Severity of Diabetes* *

Severity of Diabetes	No. of Nerves	Phospholipid, per Cent	Cholesterol, per Cent	Cerebroside, per Cent
Mild	24	1.09	0.41	0.73
Moderate	11	1.14	0.45	0.78

* Only the nerves of the lower part of the legs were studied.

TABLE 11.—*Comparison of Average Values with Respect to the Duration of Diabetes* *

Duration of Diabetes, Years	No. of Nerves	Phospholipid, per Cent	Cholesterol, per Cent	Cerebroside, per Cent
0-2	8	1.01	0.41	0.60
2-10	15	1.10	0.43	0.82
10+	13	1.13	0.43	0.72

* Only the nerves of the lower part of the legs were studied.

TABLE 12.—*Comparison of Average Values with Respect to Previous Control of Diabetes* *

Control of Diabetes	No. of Nerves	Phospholipid, per Cent	Cholesterol, per Cent	Cerebroside, per Cent
Good or fair	22	1.18	0.44	0.81
Poor	15	0.96	0.41	0.66

* Only the nerves of the lower part of the legs were studied.

The diabetic factor responsible for the neuropathy has been very elusive, as it has been in clinical studies. Severity and duration seem equally blameless, although in such a small series we hesitate to make such a definite statement. Previous control of the diabetes is apparently of some importance, but is determined with some difficulty. Rarely has the patient been under strict supervision for sufficient time for us to

know that his diabetes has been well controlled. For this reason often we are forced to accept the patient's statements as to the tests of his urine at home. The test of the urine is not an adequate index, since there may be hyperglycemia and hypercholesteremia when the urine is free from sugar.

The achilles tendon reflex in persons with diabetes shows decreased activity more often than the patellar reflex. We have compared the femoral and sciatic nerves to see if the chemical change reflects this

TABLE 13.—*Comparison of Average Values of Femoral vs. Sciatic Nerves at Pelvic Level* *

Nerve	No. of Nerves	Phospholipid, per Cent	Cholesterol, per Cent	Cerebroside, per Cent
Femoral	8	3.00	1.01	1.13
Sciatic	3	2.68	1.00	0.91

* One nerve was not labeled whether it was a femoral or sciatic nerve.

TABLE 14.—*Comparison of Lipid Values in Femoral and Sciatic Nerves in Case 11082*

Level of Nerve	Phospholipid, per Cent	Cholesterol, per Cent	Cerebroside, per Cent
Femoral	3.16	0.89	1.85
Sciatic	2.10	0.87	0.68

TABLE 15.—*Comparison of Average Values with Respect to Clinical Neuropathy* *

Reflex	No. of Nerves	Phospholipid, per Cent	Cholesterol, per Cent	Cerebroside, per Cent
Normal	2	1.24	0.41	0.47
Absent	16	1.15	0.46	0.69
Both knee jerks and both ankle jerks absent	3	0.81	0.31	0.51

* Only the nerves of the lower part of the legs were used.

TABLE 16.—*Comparison of Average Values with Respect to Clinical Neuropathy* *

Reflex	No. of Nerves	Phospholipid, per Cent	Cholesterol, per Cent	Cerebroside, per Cent
Normal	5	3.18	1.07	1.02
Sluggish	2	3.09	1.01	1.48
Absent	1	1.80	0.63	0.76

* Only the pelvic nerves were used.

disparity in function. Our values show some slight increase in pathologic change in sciatic nerves as compared with the findings in the femoral nerves, but the number of specimens is too few to lend much force to this statement.

Chemical pathologic changes, as shown in tables 15 and 16, are greater in persons with clinical evidence of marked neuropathy than in

those without clinical evidence; but the correlation, as evidenced by the values for cholesterol and cerebroside, is not close. It seems that the chemical change exceeds or precedes the clinical change to a considerable extent.

SUMMARY AND CONCLUSIONS

Analyses of various lipid constituents of fifty-two nerves from persons with diabetes and of twenty-three nerves from persons without diabetes were made.

The average phospholipid, cholesterol and cerebroside content of the nerves from diabetic patients was considerably lower than that of the nerves used for controls.

The nerves from the lower part of the legs of diabetic patients showed much greater damage than nerves from the pelvic level. This was not true in the one nerve from the lower part of the leg of a control subject as compared with the pelvic nerves from control subjects.

The greater the vascular disease in a diabetic patient the greater the damage to the nerves. In two patients without diabetes who had arteriosclerosis this pathologic change was not found, indicating that vascular disease is not the sole cause of neuropathy in diabetic patients.

Previous inadequate control of the diabetes seems to affect the nerves adversely to a slight extent. The severity and duration of the diabetes seemed not to affect the nerves, or else the effect was nullified by other factors.

The chemical pathologic changes in the nerves of diabetic patients seemed to exceed or to precede the clinical manifestations of neuropathy.

More complete studies of this chemical pathologic change to determine the effect of numerous factors are necessary before reliable statements can be made.

Progress in Internal Medicine

DISEASES OF METABOLISM AND NUTRITION

REVIEW OF CERTAIN RECENT CONTRIBUTIONS

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I. DISEASES OF METABOLISM

By Dr. Wilder

DIABETES MELLITUS

In the past year has been added what promises to be another outstanding achievement in the treatment of diabetes. This is the preparation by Hagedorn,[1] in Copenhagen, Denmark, of a compound of a protamine from salmon sperm and insulin. By virtue of a slow liberation of insulin a prolongation of the insulin effect is obtained, whereby wide fluctuations of values for blood sugar are avoided and the danger of reaction is lessened. The first printed announcement of the neo-insulin was made by Dr. Elliott P. Joslin [2] in the new edition, the fifth, of "The Treatment of Diabetes Mellitus." The information came after the manuscript of the book was completed, and the announcement appears as an added paragraph at the end of chapter 1.

The fifth edition of "The Treatment of Diabetes Mellitus" is itself a contribution of primary importance in the study of metabolism. It is more than a revision. It departs from the earlier editions in plan and organization, and while it loses thereby some of the charm, the friendly, fireside, chatty style of its predecessors, it becomes a more useful volume for study and reference. The author and his collaborators, Root, White and Marble, are to be congratulated on the systematic arrangement of

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From the Division of Medicine, the Mayo Clinic.

1. Hagedorn, H. C.: Paper read at the meeting of the Nordisk Congress for Internal Medicine, Copenhagen, Denmark, June 29, 1935. Hagedorn, H. C.; Jensen, B. N.; Krarup, N. B., and Wodstrup, I.: Protamine Insulinate, J. A. M. A. **106**:177 (Jan. 18) 1936. Root, H. F.; White, P.; Marble, A., and Stotz, E. H.: Clinical Experience with Protamine Insulinate, J. A. M. A. **106**:180 (Jan. 18) 1936.

2. Joslin, E. P.; Root, H. F.; White, P., and Marble, A.: Treatment of Diabetes Mellitus, ed. 5, Philadelphia, Lea & Febiger, 1935.

the subject matter as well as for the brevity. The pages number only 620; in the fourth edition there were 2 less than 1,000. Here at last is a treatise on diabetes worthy to take the place of the classic and heretofore unequaled second edition of the monograph of Bernhard Naunyn. Naunyn's "Der Diabetes Melitus" appeared in a second edition in 1906. Naunyn insisted on the spelling melitus, although ruefully admitting that he had few followers in this departure. The text was greatly shortened, made possible, he wrote, *weil das, was damals noch zu beweisen war jetzt längst anerkannt ist.*

What a triumphal march has been accomplished under Joslin's guidance since that time, thirty years ago! In his "Erinnerungen Gedanken und Meinungen" Naunyn [3] told of a visit by Joslin to him in Strasbourg. "It was characteristically American. Joslin wrote to ask if he might come for a brief visit. He would hardly be able to stay more than fourteen days. He came directly from Boston, with a stop of twenty-four hours in Paris. He actually remained little longer than three weeks, but the large amount of clinical material available and his great eagerness made it possible for him, in this short time, to acquaint himself with my views and principles. Then he traveled away again, directly to Boston, with a twenty-four hour stop in Paris." This was the "Naunyn period" to which Joslin so frequently refers. His patients then died of uncontrolled acidosis, which now, in the "Banting period," is preventable; but the mortality, one can be sure, was not so high as it would have been except for the influence of Naunyn. What Naunyn was at the time of the visit in Strasbourg, Joslin became—the pre-eminent authority, master and leader in the field he chose to make his own.

In a reply to an inquiry by me regarding what he considers to be the most important new data incorporated in the new book, Dr. Joslin has supplied the following comments:

Page 28, table 1: In the year 1934 with 1,396,903 total deaths were 28,000 deaths from (with) diabetes, a rate per 100,000 population of 22.1 per cent, a ratio of diabetic to total deaths of 2.0 per cent.

Page 30, table 2: Diabetes is now the tenth disease and has advanced to this place from the twenty-seventh place in 1900.

Diabetes is not an old-age disease as shown by table 9 and fig. 1. I am much interested in this fact and so, too, are the Metropolitan people [Metropolitan Life Insurance Company]. We both feel that new data should be acquired about the onset of diabetes. You know that the ordinary history by a house officer is quite unreliable. One really must have the histories taken by someone who is deeply interested in them and will recheck the original answers of patients and earnestly try to find out when the disease began.

Page 44, third line from the bottom: The proportion of diabetic deaths to the total deaths among Jews between the ages of fifty-five and sixty-four years was

3. Naunyn, Bernhard: Erinnerungen Gedanken und Meinungen, Munich, J. F. Bergmann, 1925.

11.5 per cent or, in other words, one Jew in nine Jews died with diabetes in New York City at those ages. Please note I said died *with* diabetes and not *of* diabetes. I think that phrase worth carrying into literature.

Page 48, Diabetes in twins: Umber thought so much of the importance of his three cases of twins that he wrote quite an article about it (Deutsche med. Wchnschr., 1934, no. 15). Doctor White reports our series of thirteen similar and sixteen dissimilar twins. The table on page 50 (table 15) is a rather good one.

Page 173, table 45: In this table the changes from the Naunyn era to the later Banting era, in coma, cardiorenal-vascular diseases and cancer, are of chief interest. Incidentally on page 438 you will find that of our 256 cases of cancer there were 33 instances of primary cancer of the pancreas, or 13 per cent in contrast to about 2.5 per cent and 3 per cent which are the figures generally quoted. You will note, page 438, Rothmann found cancer in 3 of 22 diabetic autopsies, but of course that was just luck. However, I think that one should stimulate people to look for cancer of the pancreas in diabetics.

Page 241, table 57: The first line shows the increased duration of diabetes in numbers at different age periods which are large enough to be of some significance.

Page 242: You will see that in the later Banting period as compared with the Naunyn period there are ten times as many diabetics living over twenty years.

Page 243: The average age at death in the Naunyn era and the late Banting era rises from 44.5 to 62.8 years.

Page 299: Exercise, I think, is increasingly helpful; the work of Richardson[4] supplements the earlier work. Long before you can remember, I know, how we all wondered why it was that some diabetic patients were helped by exercise and others not, and now, of course, the whole point appears to be that for exercise to be helpful and to lower the blood sugar, one must have insulin and if one does not manufacture his own insulin then one must inject it and then exercise.

Page 382, Friedrich's ataxia: There is an interesting article on the subject which probably merits a comment (Curins, Storring and Schomberg: Ztschr. f. d. ges. Neurol. u. Psych. **153**:719, 1935). It appears that there are ten authors in the literature who have noted a combination of Friedrich's ataxia with diabetes, a coincidence which the above authors state is too great for chance. The articles come from first-rate clinics; one of them was Umber's clinic.

Page 384: You will note that purulent infection of the urinary tract has been present in 18 per cent of 196 diabetic autopsies performed at the New England Deaconess Hospital since 1919. This last week Professor Thannhauser, in a clinic which he gave at the Boston Dispensary, emphasized the rôle of the kidney in diabetic coma. He said he thought that generally one could find some evidence of kidney involvement two or three days before the coma, and that the kidney really had much to do with the coma. Evidently he lays great emphasis on the amount of ammonia which is manufactured by the kidney.

Page 481: Fractures, I think, are worth studying. I believe they are really quite common in diabetics, but whether more common than in the non-diabetic population of similar age, I do not know. I noticed in the small group of diabetics I saw in Detroit the other day that 10 per cent had had fractures since their diabetes began. This is a subject for statistical investigation.

Page 509, table 106: Eight hundred thirty-nine diabetic children of whom 769 developed after August 7, 1922, and 70 had been seen earlier than that date, show 89 per cent survivors. One per cent has been untraced.

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4. This fact was noted in the review of last year (Wilder and Wilbur[45]).

Page 516, Dwarfism: This condition today is probably inexcusable.

Page 528: Diabetes in children surviving ten years was put in simply to stimulate other people to publish their cases so that we may know what complications are to be expected.

Page 534 gives a summary of the four preceding pages about children who either have done well, really did not have diabetes originally or were atypical cases. We cannot believe there are any cures, but stated the results in this conservative fashion.

Page 543 under section e shows data about hyper- and hypoglycemia in infants of diabetic mothers.

Page 572 calls attention to the frequency of pentosuria, and, of course, you saw the article on pentosuria in twins in the Journal of the American Medical Association (Enklewitz, M., and Lasker, M.: Pentosuria in Twins, J. A. M. A. **105**:958 [Sept. 21] 1935).

Page 573: Levulosuria has not been talked about much in this country and the paper by Silver and Reiner cited on page 573 stimulated us to hunt for a case.

These are high spots. The volume is a mine of information.

Suggestions on Therapy.—A therapeutic lead under investigation in several laboratories and clinics is what appears to be an antidiabetic activity of extracts of the mucosa of the duodenum. Ivy and Fisher [5] obtained evidence of this in 1923, as did Heller [6] in 1929. The injection of Heller's extracts in normal rabbits, prior to an injection of dextrose, prevented as marked hyperglycemia as otherwise would occur and caused the sugar content of the blood to return more rapidly to a normal or subnormal level. Laughton and Macallum [7] confirmed these observations both in dogs and in rabbits but noted that the sugar content of the blood of depancreatized dogs was not affected. In their opinion the duodenal extract acted as a stimulant to the islands of Langerhans. Heller,[8] in a recent report, names his extract duodenin. He has observed that when given by mouth it reduces the sugar content after fasting of both men and rabbits, that it is not destroyed by pepsin and acid and that by treating it with pepsin and hydrochloric acid it can be made free from secretin. La Barre and his associates [9] recently also have obtained positive results. They use the term incretin for their extract of duodenal mucosa. They noted (1) that with two dogs connected by

5. Ivy, A. C., and Fisher, N. F.: The Presence of an Insulin-Like Substance in Gastric and Duodenal Mucosa and Its Relation to Gastric Secretion, Am. J. Physiol. **67**:445 (Feb. 1) 1924.

6. Heller, H.: Ueber den blutzuckerwirksamen Stoff in Sekretinextrakten, Arch. f. exper. Path. u. Pharmakol. **145**:343, 1929.

7. Laughton, N. B., and Macallum, A. B.: Preliminary Note on Detection of Insular Hormone in Duodenum, Canad. M. A. J. **23**:348 (Sept.) 1930.

8. Heller, Hans: Ueber das insulotrope Hormon der Darmschleimhaut (Duodenin), Arch. f. exper. Path. u. Pharmakol. **177**:127, 1935.

9. La Barre, J., and Ledrut, J.: Sur l'origine pancréatique et tissulaire de l'action hypoglycémiante de l'incrétine préparée par hydrolyse pepsique, Arch. internat. de physiol. **40**:209 (Dec.) 1934.

pancreatic jugular anastomosis, that is, with the pancreatic vein of dog 1 emptying into the jugular vein of dog 2, the sugar content of dog 2 (the recipient) fell when incretin was given by vein to dog 1 (the donor); (2) that totally depancreatized dogs into which incretin was injected showed a drop in the value for sugar from levels between 225 and 310 mg. per hundred cubic centimeters to levels between 70 and 35 mg., and (3) that depancreatized dogs could be kept alive for periods of months by the oral administration of incretin, provided the doses were made three or four times as large as those necessary to produce hypoglycemia by injection. Therefore, the authors concluded that incretin both stimulates the islands of Langerhans and promotes carbohydrate metabolism in a more direct manner.

Finally, Duncan, Shumway, Williams and Fetter [10] announce results in patients. With the Macallum-Laughton extract they obtained no evidence of benefit in persons with marked hyperglycemia, but an effect became discernible when insulin was used to control the diabetes and then was omitted. Thirty patients received active extracts. In 12 the disease was called severe. In 18 it was mild. Of the 12 with severe diabetes, 8, including 4 children, showed "a definite improvement," while 4, 3 adults and 1 girl of 16, showed no benefit. Of the 18 with mild diabetes, 11 were helped and 7 were not. The protocols of these clinical observations leave one with the impression that the favorable results, in most instances, were in cases of short duration. Many investigators have fallen into this trap. They forget that it is characteristic of diabetes to show a remission during the first year or two under any kind of management and that the value of a new form of treatment must be proved with cases of long duration. This criticism is not meant to be discrediting. The results with the patients are encouraging, and the observations in the laboratories are full of promise. A serious difficulty has been encountered in the preparation of the extracts. Some have been active and others inactive.

Carrying another therapeutic suggestion for the treatment of diabetes are studies of the effect of mixtures of fractions or isolated fractions of the vitamin B complex. Funk [11] originally observed that the symptoms of vitamin deficiency in pigeons were in direct relation to the amount of carbohydrate eaten and later observed, with von Schönborn,[12]

10. Duncan, G. G.; Shumway, N. P.; Williams, T. L., and Fetter, F.: Clinical Application of Duodenal Extract (Macallum-Laughton) in Diabetes Mellitus, Am. J. M. Sc. **189**:403 (March) 1935.

11. Funk, Casimir: Studies on Beri-Beri: The Probable Rôle of Vitamines in the Process of Digestion and Utilization of Food, J. Physiol. **47**:25 (Dec. 13) 1913.

12. Funk, Casimir, and von Schönborn, Erwin: The Influence of a Vitamine-Free Diet on the Carbohydrate Metabolism, J. Physiol. **48**:328 (July 14) 1914.

that pigeons with polyneuritis showed hyperglycemia and diminution or absence of hepatic glycogen. These and other data led Mills [13] to the opinion that the requirement for vitamin B in persons with diabetes might be higher than normal and to the treatment of diabetic patients with acid-alcoholic extracts of plants. His results were about what Allen [14] obtained with myrtillin, an extract of blueberry leaves. Other investigators have made similar observations. Melcer [15] describes some benefit in 6 diabetic patients treated with the vitamin, and since then Donard and H. Labbé [16] and Binet, Fabre and Bargeton [17] have written on the subject. M. Labbé, Nepveux and Gringoire [18] have used a product of vegetable origin, said to be four times as strong in vitamin B activity as dried brewer's yeast of good quality. When fed to normal rabbits in doses of 15 Gm., it caused an increase in the stores of glycogen and glutathione of 140 and 30.5 per cent, respectively. When it was given to diabetic patients, it had little effect in 2, a stabilizing action on the sugar content in 1 and a favorable effect on the tolerance for carbohydrate in 9. The average increase in tolerance was equivalent to 46 Gm. of dextrose. The protocols of these observations are not at hand, and hence it is impossible to evaluate the results. They appear to have much the same significance as those made by Mills.[13]

Von Drigalski [19] recently reviewed the literature on this subject and reports 10 cases of diabetes in which the patients were treated with yeast. He concludes that yeast has no influence on the glycosuria, acidosis, concentration of sugar in the blood, requirement for insulin or body weight of patients who have diabetes. He expresses the opinion that in persons with diabetes conditions are entirely different from

13. Mills, C. A.: Treatment of Diabetes with an Acid-Alcohol Extract of Plants Rich in Vitamin B, Am. J. M. Sc. **175**:376 (March) 1928.

14. Allen, F. M.: Blueberry Leaf Extract: Physiologic and Clinical Properties in Relation to Carbohydrate Metabolism, J. A. M. A. **89**:1577 (Nov. 5) 1927.

15. Melcer, A. S.: Treatment of Diabetes with Vitamin B, Polska gaz. lek. **11**:89 (Jan. 31) 1932.

16. Donard, E., and Labbé, H.: Sur l'existence, dans les touraillons d'orge germée, d'une substance ayant un pouvoir hypoglycémique et agissant d'une façon analogues à l'insuline, Compt. rend. Acad. d. sc. **194**:1299 (April 18) 1932.

17. Binet, L.; Fabre, R., and Bargeton, D.: Pouvoir hypoglycémiant d'un extrait aqueux de levure de bière, Compt. rend. Soc. de biol. **113**:235, 1933.

18. Labbé, Marcel; Nepveux, Floride, and Gringoire, J. D.: Le rôle des vitamines B dans le métabolisme hydrocarboné: Leur emploi dans le traitement du diabète, Bull. Acad. de méd., Paris **109**:689 (May) 1933; Influence des vitamines B sur la teneur en glycogène et en glutathion du foie des lapins, J. de méd. de Paris **53**:501 (June 8) 1933; Compt. rend. Soc. de biol. **133**:152 (May) 1933. Gringoire, J. D.: Les vitamines B: Leur rôle dans le métabolisme hydrocarboné. Leur emploi dans le traitement du diabète, Paris, E. Le François, 1933.

19. von Drigalski, W.: B-Vitamine als Insulinersatz, Arch. f. Verdauungskr. **57**:1 (Jan.) 1935.

those which obtain in experimental animals, which show an influence of vitamin B on carbohydrate metabolism. In the meantime, however, Williams and his associates [20] have prepared pure crystalline vitamin B_1, and in a preliminary report on the use of this, in doses of 10 mg. a day, 5,000 international units, they state that favorable effects on tolerance were observed. The protocols are not given, and if the condition was in the early stages confirmatory observations must be obtained in cases of severe diabetes of long duration before much emphasis can be placed on the reputed results. Recent personal observations on the effect of crystalline vitamin B_1 in 6 "pedigreed" cases of long duration have not been very encouraging, but it seems not unlikely that some additional supply of vitamin B, particularly B_1, may be distinctly beneficial, if not on the tolerance for carbohydrate at least on the general health of the patient. The large vegetable content of the diets of many diabetic patients is no guarantee that the supply of this indispensable food factor is adequate to provide for an organism which, like that of the polyneuritic pigeon, is handicapped in the matter of handling dextrose.

The attempt to affect the tolerance for carbohydrate by treatment directed at the pituitary gland was considered in the review last year. Merle [21] described the case of a woman 31 years of age with diabetes resistant to insulin. The glycosuria was more marked at the time of menstruation; an endocrine antagonist to insulin was suspected, and the pituitary was irradiated from both sides in eight treatments, two each week. The total dose corresponded approximately to one-third the sterilizing dose for the ovary. The output of sugar was less after this treatment than it had been possible to obtain before, even with large doses of insulin. Soskin, Mirsky, Zimmerman and Crohn [22] have attempted the clinical application of the observations of Barnes and his associates [23] on the inhibitory effect of estrogenic hormone on the anterior lobe of the pituitary. The results were the same as those with

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20. Vorhaus, M. G.; Williams, R. R., and Waterman, R. E.: Studies on Crystalline Vitamin B_1: Experimental and Clinical Observations, J. A. M. A. **105**:1580 (Nov. 16) 1935.

21. Merle, E.: Diabète grave insulino-résistant: Réduction brusque et massive de l'insulino-résistance par irradiation de la région hypophysaire, Bull. et mém. Soc. méd. d. hôp. de Paris **51**:35 (Jan. 21) 1935.

22. Soskin, Samuel; Mirsky, I. A.; Zimmerman, L. M., and Crohn, N.: The Rôle of the Anterior Pituitary Gland in Pancreatic Diabetes and Diabetes Mellitus, Am. J. Physiol. **113**:124 (Sept.) 1935.

23. (*a*) Barnes, B. O.; Regan, J. F., and Nelson, W. O.: Improvement in Experimental Diabetes Following the Administration of Amniotine, J. A. M. A. **101**:926 (Sept. 16) 1933. (*b*) Barnes, B. O.; Culpepper, W. L., and Hutton, J. H.: Experimental Diabetes Treated by X-Ray Applied to the Pituitary and Adrenal Regions, Am. J. Physiol. **113**:7 (Sept.) 1935.

the dogs: The well-being of the patients could be maintained when the administration of insulin was entirely omitted, and there was some "temporary alleviation of the hyperglycemia and glycosuria." Even in the presence of hyperglycemia and glycosuria no ketone bodies appeared in the urine. This is less encouraging than might have been expected. The work of Selle, Westra and Johnson [24] fails entirely to confirm the observations of Hutton,[25] mentioned last year, and those of Barnes and his associates reported more recently.[23b] In five of seven diabetic depancreatized dogs the sugar content of blood drawn before breakfast was not reduced after irradiation of the pituitary, and no indication was found that the severity of the symptoms was diminished. The authors call attention to the fact that the conditions of the experiments are different from those in subjects with spontaneous diabetes. Their results, nevertheless, "sound a note of warning to workers contemplating the treatment of diabetes mellitus by irradiation of the hypophysis." They administered massive doses, such as one would not employ in treating a patient, doses three times enough to cause severe second degree burns if applied to the skin, and the degree of damage from such treatment to nerve structures and the other hormones of the hypophysis is conjectural. They express the opinion that a better rationale must be had before treatment of diabetes by irradiation can be indorsed.

Effects of Salts of Sodium and Potassium in Carbohydrate Metabolism.—The existence of a reciprocal relationship between the metabolism of chlorides and that of dextrose has been suggested by various observations, such as the lower than normal levels, frequently, of chloride in the blood of persons with diabetes and the higher than normal levels, frequently chloride in the blood of persons with some states of hypoglycemia. Also, when the chloride content of the blood is diminished, as occurs for instance with obstruction of the upper portion of the intestines or after the injection of histamine, the sugar content is said to rise. In consequence, Glass and Beiless [26] were led to study the effect in persons with diabetes of the injection of hypertonic solutions of sodium chloride. Schenk [27] had observed that the level of sugar fell after the injection of 100 cc. of a 10 per cent solution of sodium chloride but had attributed it to dilution of the blood. Glass and Beiless, into

24. Selle, W. A.; Westra, J. J., and Johnson, J. B.: Attempts to Reduce Symptoms of Experimental Diabetes by Irradiation of Hypophysis, Endocrinology **19**:97 (Jan.-Feb.) 1935.

25. Hutton, J. H., quoted by Wilder and Wilbur.[45]

26. Glass, J., and Beiless, I.: Chlorhaushalt und Kohlenhydratstoffwechsel: Einfluss hypertonischer Kochsalzlösung auf den Blutzuker bei Diabetes, Ztschr. f. d. ges. exper. Med. **73**:801, 1930.

27. Schenk, quoted by Glass and Beiless.[26]

10 diabetic patients, injected intravenously from 3 to 4 Gm. of chemically pure sodium chloride in a 15 to 20 per cent solution and observed with great regularity that the values for sugar fell. The drop was from 12 to 43 per cent, averaging 25 per cent, of the original dextrose content of the blood. Hyperglycemia produced by the administration of dextrose was affected in a similar manner. Like results were obtained in 4 nondiabetic patients, although the effect in them was less striking. Sodium chloride by mouth in a dose of 12 Gm. was equally efficacious. The results could not be explained by spontaneous fluctuations or by dilution of the blood. They were attributed to the chloride anion rather than to the sodium cation, because reported depressions of the sugar content of the blood following injections of sodium bicarbonate had never been of such significance. A vagotonic action on the part of the sodium chloride was suggested in explanation.

A much more elaborate study of the subject has been made by McQuarrie, Thompson and Anderson.[28] Two children with diabetes possessed an inordinate craving for table salt and required between 60 and 90 Gm. daily to satisfy this craving. On account of this, 1 of the children, 3 other diabetic patients without the unusual craving, and 1 normal subject, all in the age group between 13 and 15 years, were subjected to the following investigation: They were given pure sodium chloride by mouth in doses of from 1 to 2 Gm. per kilogram of body weight per day, with the result, in a period of from two to four days, that the body weight increased from 4 to 5 per cent, that the blood pressure rose to new plateaus between 30 and 50 per cent above former levels and, in the case of the diabetic patients, that the degree of glycosuria was markedly diminished and the sugar content of the blood before breakfast was brought down to considerably lower levels. The intake of food, dosage of insulin and activity remained unchanged. In the diabetic subjects the respiratory quotient before breakfast was slightly higher during the period of high intake of sodium chloride, ketonuria produced by the omission of insulin appeared later and the nitrogen balance, which previously had been negative, became positive, evidence of improved utilization of carbohydrate.

The sodium cation rather than the chloride anion was thought to be responsible for the phenomena observed by McQuarrie and his asso-

28. McQuarrie, Irvine: The Effects of Excessive Salt Ingestion on Carbohydrate Metabolism and Arterial Pressure in Diabetic Children, Proc. Staff Meet., Mayo Clin. **10**:239 (April 10) 1935. McQuarrie, Irvine; Thompson, W. H., and Anderson, J. A.: Effect of Excessive Ingestion of Sodium and Potassium Salts on Carbohydrate Metabolism and Blood Pressure in Diabetic Children, J. Nutrition, to be published. Thompson, W. H., and McQuarrie, Irvine: Effects of Various Salts on Carbohydrate Metabolism and Blood Pressure in Diabetic Children, Proc. Soc. Exper. Biol. & Med. **31**:907 (May) 1934.

ciates, because sodium bicarbonate and sodium citrate, when given in amounts with equivalent sodium values, had similar even though less marked effects than those of sodium chloride. Also, the potassium cation was found to exert an opposite action. An ordinary diet high in potassium either prevented or greatly lessened the effects of sodium chloride, and potassium chloride in doses of from 10 to 20 Gm. daily, together with a simplified diet low in sodium, resulted in a fall in blood pressure and a significant increase in the degree of glycosuria. When the two salts were administered together, one part of potassium was found to abolish completely the effects of at least three chemically equivalent parts of sodium. Attention is directed to the high values for potassium in the blood serum occasionally noted in untreated persons with diabetes mellitus. Only a few determinations of potassium have been made in the present study, but these indicate that high ingestion of sodium chloride is followed by a significant decrease of potassium in the serum, similar to that which occurs after the injection of insulin. This part of the study is as yet incomplete.

MacLean [29] likewise reported on the action on the carbohydrate metabolism of large doses of sodium chloride. A patient with relative insensibility to insulin, attributable to infected gangrene of a foot, received 40 Gm. after each meal for three doses. That night a severe reaction to insulin occurred, and during the next fourteen days the requirement of insulin steadily declined from 115 to 55 units a day. Additional personal experience has led me to consider that saline therapy in persons with diabetes may be efficacious with doses of salt that are considerably smaller than those used by McQuarrie but that the usefulness of the procedure will lie principally in the management of patients with relative insensitivity to insulin. In the well controlled case of a patient with severe but uncomplicated diabetes of ten years' duration, 15 Gm. "extra" of ordinary table salt a day resulted in a fall of the requirement of insulin from a daily dose of 60 units to one of 40 units. The indication for reducing the dosage was the development of symptoms of reaction to insulin, but after about a week the requirement rose again to the original figure. On the other hand, in recent months I have seen repeatedly a favorable and lasting effect on patients who were insensitive to insulin because of infection or other complications. The subject is one which deserves much study, with particular attention paid to the balance of the sodium and potassium ions of the blood.

The Diet for Patients with Diabetes.—The subject of what constitutes an optimal diet for the patient with diabetes continues to occupy the center of the stage, as it has since John Rollo first resorted to diet as a means

29. MacLean, A. R.: Observations on Administration of Sodium Chloride in Diabetes, Proc. Staff Meet., Mayo Clin. **10**:321 (May 22) 1935.

of controlling the output of sugar in the urine. The pendulum swings now this way and now that, with reasonable arguments advanced for every departure. The subject was recently reviewed by Cardle,[30] and some of what follows is a part of the substance of his address. The two opposing extremes of dietary procedure were compared, the so-called high fat and the so-called high carbohydrate diets. In the procedure involving extreme limitation of carbohydrate, as first recommended by Petrén and almost simultaneously and independently by Newburgh and Marsh, emphasis was placed on the rigid restriction of protein. The calories were adequately supplied by fat, and it was found that nutrition could be maintained, acidosis avoided and hyperglycemia diminished. In a recent study Newburgh and Waller[31] showed that the tolerance of a diabetic patient, namely, the maximal capacity to dispose of the available dextrose from all sources without glycosuria in the absence of insulin, is not depressed by fat in the diet or augmented by carbohydrate in the diet and that the continued administration of the high fat content of maintenance diets does not lower it. In their opinion the efficiency of insulin in the human diabetic subject, as in the depancreatized dog, is related to the total amount of dextrose on which it acts. When the amount of available dextrose far exceeds the amount tolerated, each unit of insulin will cause the oxidation of 6 or 7 Gm. of dextrose. Under otherwise similar conditions, except for a small excess of available dextrose, only 1 or 2 Gm. is oxidized per unit of insulin. It has been the experience of Newburgh and Waller that 3 of every 4 diabetic patients can tolerate a diet high in fat and maintain themselves in a satisfactory state of nutrition without the use of insulin.

The divergent procedure, the diet high in carbohydrate and low in fat, has an ancient history. In 1500 B. C. an Egyptian prescription designed "to draw away the passing of too much urine" called for "a concoction of cakes, wheat grains, fresh grits, honey, sweet beer and berries." In the seventeenth century Willis advocated milk, rice and starch. The rice cure of von Düring came in 1868 and the potato diet of Mossé in 1898. Von Noorden's oatmeal cure and the combined cereal cure of Falta followed. The introduction of insulin brought with it the possibility of controlling glycosuria with diets of any type, and Geyelin, independently Sansum, soon afterward Porges and Adlersberg and later Rabinowitch and others proceeded to take the fullest advantage of the new substitution therapy. These authors have all convinced

30. Cardle, A. E.: The Diabetic Diet, read before the Minnesota Society of Internal Medicine, Minneapolis, Nov. 11, 1935.

31. Newburgh, L. H., and Waller, Dorothy S.: Studies of Diabetes Mellitus: Evidence that the Disability Is Concerned Solely with the Metabolism of Glucose; the Mode of Action of Insulin, J. Clin. Investigation **11**:995 (Sept.) 1932.

themselves of the desirability of their procedures, claiming that the well-being of the patient is improved, that a positive nitrogen balance is maintained more easily, that the danger of acidosis is diminished, that the tolerance for carbohydrate is improved and that the progress of arteriosclerosis is impeded. Mention was made in last year's review of Geyelin's report in the symposium of the New York Academy of Medicine. Since then he [32] has published a more extended account of his experience. Tuberculosis associated with diabetes was either cured or arrested in 21 of 26 patients. It has been impossible to secure follow-up records of all his 900 cases of diabetes in which treatment has been given during the past ten years, but in no patient who is at present under observation and in none of those who have been heard from has tuberculosis developed. Geyelin attributes this relatively low incidence of tuberculosis and also a relatively low incidence of gangrene and cardiovascular disease to the diet high in carbohydrate, but in the conclusion he adds the significant words, "normal calories." Geyelin's diets, in contrast to those in many clinics, are relatively high in caloric value, and this I think may contribute a great deal to his good results. Lukens [33] also believes that treatment has been improved by provision of a liberal allowance of carbohydrate, and Adlersberg,[34] who with Porges advocated a diet rich not only in carbohydrate but also in protein, again recounts the advantages to be obtained by this procedure. The addition of fat, he maintains, affects the metabolism unfavorably, even if the number of calories is not increased.

These reports are impressive, but like many clinical studies they do not provide conclusive evidence of the correctness of the views of their authors. If diabetic patients could be shut up in cages and fed strictly according to theoretical indications for a sufficient number of years, satisfactory answers might be obtained. As it is, I can claim with equal justification that the patients at the Mayo Clinic are doing just as well as those of Geyelin or Rabinowitch, if not better. My associates and I too have observed almost no tuberculosis and surprisingly little arteriosclerosis. There has been practically no arteriosclerosis in our young patients. The results of surgical procedure in our diabetic patients [35] certainly are as satisfactory as those to which Adlersberg refers, while

32. Geyelin, H. R.: The Treatment of Diabetes with Insulin (After Ten Years), Contrasting the Effects of Normal and of the Older Diabetic Diets, J. A. M. A. **104**:1203 (April 6) 1935.

33. Lukens, F. D. W.: Carbohydrate in Diabetes: Newer Conceptions of Its Use, Pennsylvania M. J. **37**:992 (Sept.) 1934.

34. Adlersberg, D.: Le régime pauvre en graisses dans le diabète simple (sans dénutrition), Bull. gén. de thérap. **186**:58, 1935.

35. Walters, Waltman; Meyerding, H. W.; Judd, E. S., and Wilder, R. M.: Surgery in Diabetes, Minnesota Med. **17**:517 (Sept.) 1934.

consistently for many years we have been prescribing diets that contain not over 110 Gm. of carbohydrate, 70 Gm. of protein and a good deal of fat. Like Geyelin, we have always insisted on adequate nutrition. The caloric requirement of the individual patient has been based on the assumption that the white collar worker and the housewife require food in an amount to exceed the basal caloric requirement for twenty-four hours by 50 per cent. Most of these calories come from fat, and therefore in many cases the amount of fat will equal or exceed 200 Gm. The diets are palatable, and the patients like them. They adhere to them with surprising faithfulness, and occasionally when we have tried to change to a diet high in carbohydrate in an individual case, the patient has objected.

Cholesterol and Arteriosclerosis.—The high incidence of arteriosclerosis in diabetic persons, together with the frequent occurrence of elevated values for cholesterol and other lipoids in this disease, has induced some clinicians, particularly those who advocate diets high in carbohydrate, to conclude that the arteriosclerosis of diabetes is a result of feeding diets rich in fat. These clinicians have been influenced by the imbibition theory of Virchow as amplified by the Russians Anitschkow and Chalatow as well as by Aschoff. The subject of cholesterol and arteriosclerosis is exhaustively reviewed by Duff [36] of the department of pathology at the Johns Hopkins Hospital, with the following conclusions: The production of arteriosclerosis in rabbits by feeding cholesterol, as demonstrated by Anitschkow and Chalatow in 1913 and subsequently repeatedly confirmed by others, is not a valid reason for believing that an excess of cholesterol in the diet plays a part in the etiology of arteriosclerosis in man. The lesion produced in the rabbit is not identical anatomically with that of arteriosclerosis in man. The lesion in the rabbit involves the media primarily. The intima is first to be affected by the disease in man. The lesion in the rabbit is always dependent on hypercholesteremia, whereas hypercholesteremia is not observed with any regularity in human subjects with arteriosclerosis. The lesion in the rabbit is always associated with deposits of cholesterol in other organs and tissues; this has no counterpart in the arteriosclerosis of man. A uniform failure has accompanied all attempts to produce arterial lesions by feeding cholesterol to animals the diets and cholesterol levels of which are more comparable to those of man: cats, dogs, foxes and monkeys. This negative evidence is more important for application to human conditions than is the positive evidence from the experience with rabbits. Finally, those pathologic conditions in man which are associated with cholesteremia, with the one exception diabetes, are infre-

36. Duff, G. L.: Experimental Cholesterol Arteriosclerosis and Its Relationship to Human Arteriosclerosis, Arch. Path. **20**:81 (July); 259 (Aug.) 1935.

quently associated with arteriosclerosis. Duff refers to pregnancy, hypothyroidism, obstructive jaundice, certain types of nephritis and lipoid nephrosis. These negative observations in patients with outspoken hypercholesteremia constitute the strongest sort of evidence against the idea that hypercholesteremia acting alone can cause arteriosclerosis. On theoretical grounds it might accelerate the development of arteriosclerotic changes previously initiated by some other agent, but there is little evidence at present that it plays even this small rôle.

These also are the conclusions of Weiss and Minot.[37] According to them, the evidence which has been brought forward in the attempt to demonstrate the relationship between the cholesterol content of the diet and the development of arteriosclerosis in man is equivocal and therefore not convincing. Indeed, it would hardly influence an opinion not already prejudiced in favor of the idea. The recent paper by Watson and Wharton [38] leads to the same conclusions. These authors studied 112 dietary combinations as applied in 27 cases of diabetes and did not observe any significant disturbance of the cholesterol content of the blood, even with fairly extreme variations of the content of the diets in fat.

Diabetes admittedly is a disease in which hyperlipemia and hypercholesteremia frequently are associated, but the metabolic disturbance of diabetes is by no means confined to the metabolism of lipoids. Hyperglycemia, ketosis or the frequent occurrence of infections can just as well be held responsible for the arteriosclerosis in this disease. Periodic dehydration, the frequency with which diets are inadequate in certain nutritional factors, such as some of the vitamins and salts, and the possibility that patients with diabetes require more than a normal supply of certain vitamins are other possible explanations. Nor is it clear that the severity of the arteriosclerotic changes in persons with diabetes parallels the degree of elevation of the lipoids in the blood. In a series of cases studied by Hunt [39] the most advanced arteriosclerotic changes appeared in the patients whose average cholesterol levels had been lowest. Bearing on this general problem of arteriosclerosis is a recent report on the physical condition of Vilhjalmur Stephansson, the arctic explorer, who for eleven and a half years lived within the arctic circle and for a number of days totaling nine years was on an exclusive meat

37. Weiss, Soma, and Minot, G. R.: Nutrition in Relation to Arteriosclerosis, in Cowdry, E. V.: Arteriosclerosis: A Survey of the Problem, New York, The Macmillan Company, 1933, p. 233.

38. Watson, E. M., and Wharton, Marion A.: A Comparison of Various Diets in the Treatment of Diabetes Mellitus, Quart. J. Med. **4**:277 (July) 1935.

39. Hunt, Hazel M.: Cholesterol in Blood of Diabetics Treated at the New England Deaconess Hospital, New England J. Med. **201**:659 (Oct. 3) 1929.

diet. Lieb [40] reports extensive clinical and laboratory studies of Mr. Stephansson and of another arctic explorer, who were placed on an "arctic" diet consisting exclusively of meat. The observations were made in the Russell Sage Foundation at Bellevue Hospital and continued for a full year in 1929. Stephansson's diet averaged about 2,650 calories; 2,100 of these consisted of fat and 550 of protein. The amount of carbohydrate in the meat varied between 30 and 50 calories a day. At this time the chemical composition of the blood was normal except for higher lipoid values than ordinarily are regarded as normal. Since 1922, Dr. Lieb has made an annual examination of Mr. Stephansson, and the last of these is the subject of the present report. Mr. Stephansson, although he is now 55 years of age, has remained in excellent general health and has gained in weight to 84 Kg. as compared to 70.8 Kg. in 1922. The examination revealed no significant abnormalities. The blood pressure was 120 mm. systolic and 80 diastolic; the eyegrounds were normal, and the arteries, aside from "slight radial thickening," apparently were normal.

Questionnaire on Diabetes.—In the *Medizinische Klinik* a number of outstanding clinicians, Falta [41] of Vienna, Schmidt of Prague, Umber of Berlin, Katsch of Griefswald and Porges of Vienna, supply brief answers to a number of stated questions, as follows: 1. Is the abnormality of the islands of Langerhans sufficient in every case of diabetes to account for the disease? 2. Are there various forms of diabetes? 3. May extra-insular diabetogenic factors alone provoke diabetes, or do they merely modify the clinical picture of the disease? 4. Is there an optimal diet for patients regularly receiving insulin? 5. Does muscle work modify the dextrose equivalence of insulin? 6. Does the symptom complex of spontaneous hypoglycemia depend on increased function of the island mechanism? 7. Are there any hormones besides insulin that are useful in the treatment of diabetes? The opinions on several of the topics vary as widely as would be expected. The answers nevertheless are interesting and instructive. On the subject of the diet, Porges' views are those of Adlersberg, previously mentioned. Katsch, Umber and Schmidt are of the opinion that the diet should be adjusted to the food habits and social status of the patient. Falta says that the optimal diet is that which best fits the individual patient. Since the requirement of insulin depends on the carbohydrate and protein content of the food, these must be held constant, but the amount of fat can vary within wide limits without great influence on the dose of insulin. There-

40. Lieb, C. W.: A Year's Exclusive Meat Diet and Seven Years Later, Am. J. Digest. Dis. & Nutrition **2**:473 (Oct.) 1935.

41. Falta, W.: Das endokrine System in der Pathologie und Therapie des Diabetes, Med. Klin. **31**:10 (Jan.) 1935.

fore, one may leave the selection of the amount of fat to the appetite, the intake of calories being adjusted automatically. In some instances, however, mostly in those in which the equivalence of insulin in dextrose is low, a rich allowance of carbohydrate increases the equivalence, and the addition of fat depresses it. In such a case a diet high in carbohydrate may be used with advantage.

The Theory of Diabetes.—The theory of diabetes upheld by Naunyn, Minkowski and Lusk, which regards failure in the metabolism of dextrose as the underlying disturbance in this disease, has been under attack from the beginning and continues so. Pflüger and von Noorden, Geelmuyden, Macleod and many others have crossed swords with its advocates. Now come Soskin,[42] a former pupil of Macleod, and his associates, with an extensive series of experimental observations supporting the alternate theory of glyconeogenesis.[42d] As I interpret the results, they show conclusively that the stability of the glycogen stores of the liver and possibly the rate of glycogenesis from protein are susceptible of modification by a variety of influences other than that exerted by insulin; they do not bear crucially on the all-important question of whether the large amount of sugar excreted by the diabetic organism is sugar made de novo from fatty acid. That is, they do not show that the liver can make more sugar than may be accounted for by glycogen, protein, lactic acid and glycerin. The experiments are ingenious, and it is extremely interesting that depancreatized dogs into which insulin and dextrose are injected continuously to maintain a constant blood sugar level react like normal dogs to the injection of extra sugar; the extra sugar causes a characteristic elevation of the blood sugar level, followed by a fall to below the "normal" level, exactly as occurs in the course of a dextrose tolerance test in a normal dog or man. This result upsets the idea that the dextrose tolerance test is a measure of the response of the pancreas and shows that the curves for the sugar content of the blood obtained in dextrose tolerance tests are imperfect indexes of the production of insulin.

In this connection research is reported by Ellis[43] of the Medical Unit, the London Hospital. Patients with severe diabetes were given

42. (*a*) Soskin, S.: Utilization of Carbohydrate by Totally Depancreatized Dogs Receiving No Insulin, J. Nutrition **3**:99 (Sept.) 1930. (*b*) Soskin, S., and Allweiss, M. D.: Hypoglycemic Phase of Dextrose Tolerance Curve, Am. J. Physiol. **110**:4 (Nov.) 1934. (*c*) Soskin, S., and Mirsky, I. A.: The Influence of Progressive Toxemic Liver Damage upon the Dextrose Tolerance Curve, ibid. **112**:649 (May) 1935. (*d*) Soskin, S.; Allweiss, M. D., and Mirsky, I. A.: Interpretation of Abnormal Dextrose Tolerance Curves Occurring in Toxemia in Terms of Liver Function, Arch. Int. Med. **56**:927 (Nov.) 1935.

43. Ellis, Arthur: Increased Carbohydrate Tolerance in Diabetics Following the Hourly Administration of Glucose and Insulin Over Long Periods, Quart. J. Med. **3**:137 (April) 1934.

dextrose at hourly intervals over periods of days, receiving no other food. Insulin was injected hourly. Although 600 Gm. of dextrose a day was ingested in this manner, the dose of insulin required did not exceed that necessary with an ordinary restricted diet and in some cases was less. How is this to be explained? The observation is analogous to that referred to by Woodyatt [44] in the symposium of the New York Academy of Medicine mentioned in last year's review.[45] Ellis offers no explanation and nevertheless regards the observations as "difficult to reconcile with the generally accepted theory of pancreatic 'exhaustion.'" Soskin's [42a] explanation would be that the "homeostatic regulation of the liver" was set at a higher level by the treatment with dextrose, so that the rate of endogenous production of sugar was diminished. Himsworth [46] would say that the amount of insulin kinase produced by the liver was increased, so that less insulin went farther. To my mind the subject is linked with that of sensitivity to insulin.

Complications of the Eye in Diabetes.—Waite and Beetham [47] have compared observations on the eyes of 2,002 diabetic patients from the New England Deaconess Hospital with those on the eyes of 457 non-diabetic controls. The patients were selected consecutively as they were admitted to the hospital. The summary and conclusions are as follows: Patients with diabetes showed a high incidence of wrinkles in Descemet's membrane (patients with diabetes, 26 per cent; controls, 10 per cent), of deep retinal hemorrhage (patients with diabetes, 18 per cent; controls, 3 per cent) and of depigmentation of the epithelium of the iris (patients with diabetes, 6 per cent; controls, 2 per cent). On the other hand, the incidence of cataract of all varieties, except flocculi in patients with juvenile diabetes, was not greater in the diabetic persons. An equal incidence was noted also for iritis, atrophy of the optic nerve and arcus.

Paresis of accommodation was demonstrated in 21 per cent of the diabetic patients; it was transitory, improving with treatment. An explanation may be that the deposition of glycogen in the pigment epithelium of the ciliary body hampers accommodation; on the other hand, frequent association with transitory changes in refraction suggests that alterations of the lens play a part. Abnormal deposits of glycogen

44. Woodyatt, R. T., quoted by Wilder and Wilbur.[45]

45. Wilder, R. M., and Wilbur, D. L.: Diseases of Metabolism and Nutrition: Review of Certain Recent Contributions, Arch. Int. Med. **55**:304 (Feb.) 1935.

46. Himsworth, H. P.: The Activation of Insulin, Lancet **2**:935 (Oct. 29) 1935.

47. Waite, J. H., and Beetham, W. P.: Visual Mechanism in Diabetes Mellitus: Comparative Study of Two Thousand and Two Diabetics, and Four Hundred and Fifty-Seven Non-Diabetics for Control, New England J. Med. **212**:367 (Feb. 28); 429 (March 7) 1935.

were observed repeatedly in the retina, in the optic nerve, in the epithelium of the capsule of the lens and especially in the pigment epithelium of the iris and the ciliary body. The ciliary body in some cases was increased to many times its normal thickness by glycogen alone.

Transitory changes of refraction occurred in 6 per cent of the patients with diabetes. The errors of refraction were usually less than 2 diopters; the maximal change was 8 diopters. The changes did not occur in eyes from which the lens had been removed, aphakic eyes. The explanation is not wholly to be found in the sugar of the ocular fluids. The authors cite Granstrom as having demonstrated that the radius of the cornea is not altered and that no shortening or lengthening takes place in the axis of the globe. The disturbance is believed to be in the index of refraction of the lens, which is dependent on the retention of salt and the interplay of osmotic forces following precipitate shifts of the level of sugar in the blood.

TABLE 1.—*Retinal Abnormalities (After Waite and Beetham*[47])

	Visible Fundi in 3,915 Diabetic Persons Examined		Visible Fundi in 101 Nondiabetic Persons Examined	
	Number	Percentage	Number	Percentage
Deep retinal hemorrhages	730	18.6	34	3
Waxy exudates	420	10.7	7	0.7
Hemorrhage of nerve fiber layer	196	5.0	33	3
Cotton wool exudates	168	4.3	35	3
Iridescent crystals	28	0.7	4	
Proliferation of capillaries	26	0.7		

Senile and complicated cataracts occurred with no more frequency in the diabetic patients than in the nondiabetic persons, but cataracts were noted in 11 of 297 children. The characteristics in these juvenile cases, fine flocculi and iridescent crystals in the cortical levels, with later changes in the posterior cortex at the pole, were like those of the cataracts associated with parathyroid tetany, scleroderma and myotonic dystrophy.

The principal abnormalities of the retina and the incidence of these are shown in table 1.

Another recent study of diabetic retinitis is that of Wagener, Dry and Wilder.[48] The authors have compared observations in a series of 1,052 consecutive cases of diabetes, with the examination of the eyes made usually by one examiner (Wagener). Various types of hemorrhagic lesions of the fundus are described, with retinal photographs to illustrate

48. Wagener, H. P.; Dry, T. J., and Wilder, R. M.: Retinitis in Diabetes, New England J. Med. **211**:1131 (Dec. 20) 1934.

them. The relative frequency of these types is indicated in table 2. It will be noted that the incidences of hemorrhagic lesions of all varieties are in fairly close agreement with those reported by Waite and Beetham.[47] The lesions occur predominantly in patients more than 40 years of age and usually, but not always, are associated with hypertension or other evidence of general vascular disease. Waite and Beetham observed that the lesions multiply with the continuation of diabetes but are not related to the age of the patient or to sclerosis of retinal vessels, vascular hypertension or renal disorders. They also demonstrate an absence of correlation with the dosage of insulin or the sugar content or calcium content of the blood. Wagener, Dry and Wilder comment on the frequency of the condition as compared with that observed in 1921 by Wagener and Wilder [49] (17.7 per cent in this study; 12.3 per cent in

TABLE 2.—*Incidence of Retinitis in One Thousand and Fifty-Two Cases of Diabetes (After Wagener, Dry and Wilder* [48])

Type	Male	Female	Total	Incidence, per Cent
A. Typical of hypertension, not diabetic	4	8	12	1.1
B. Diabetic				
1. Hemorrhages only	32	26	58	5.5
2. Hemorrhages with punctate exudates	32	35	67	6.3
3.* Hemorrhages with punctate and cotton-wool-like exudates	15	16	31	2.9
4a. Venous disease without proliferation	5	6	11	1.1
4b.† Venous disease with proliferation	3	5	8	0.8
Total	91	96	187	17.7

* This type represents the retinitis centralis punctata diabetica of Hirschberg.
† This type is the full-blown retinitis proliferans.

the earlier study). This is accounted for by the longer lives at present of patients with diabetes. They lay particular stress on the finding of 23 patients (12 per cent of all diabetic patients who had hemorrhagic lesions of the retina) in whom retinitis developed in the absence of all clinical evidence of vascular disease. The lesion is usually mild in cases in which the condition is uncomplicated with other vascular disease, but its very existence must mean that the diabetes does something to injure the finer arterioles or venules of the retina.

In the series of Wagener, Dry and Wilder there were 66 patients whose eyes were examined two or more times over a period of several years, and from a study of the observations it appears likely that the retinal disease in question passes progressively through successive stages, beginning with hemorrhages only and eventuating in evident disease of the veins. The rate of progression is variable. Remissions

49. Wagener, H. P., and Wilder, R. M.: The Retinitis of Diabetes Mellitus: Preliminary Report, J. A. M. A. **76**:515 (Feb. 19) 1921.

occur occasionally, but the final stage is that marked by proliferative changes and hemorrhage into the vitreous, the so-called retinitis proliferans. It is suggested that the retinal vessels suffer injury in all cases of diabetes but that in four fifths of all cases the injury is insufficient to give rise to discernible hemorrhage or exudation. When the vessels are previously affected by other disease—nephritis, hypertension or atherosclerosis—it is more likely to do so. In that case a lesion characteristic of diabetes (punctate hemorrhages, deep exudates or visible disease of the larger retinal veins) is added to a retinal vascular lesion, otherwise characteristic of hypertension, arteriosclerosis or nephritis. The trained observer can diagnose diabetes correctly from the appearance of the retinal lesion whether this is simple or superimposed on a retinal abnormality produced by other conditions.

TREATMENT OF THINNESS WITH INSULIN

The frequency with which hunger is precipitated when the sugar content of the blood falls during a reaction to insulin led to the thought that appetite might be stimulated with insulin in patients with anorexia and to the use of insulin for this purpose. In 1923 Pitfield [50] reported satisfactory results from treatment with insulin in 2 cases of infantile inanition; in 1924 Marriott [51] and Barbour [52] noted gains in weight in malnourished infants, and in 1925 Falta [53] reported on the use of the method in malnourished adults. In later papers Falta [41] expressed the view that the advantage was not entirely attributable to the improved appetite and suggested that insulin also favored the deposition of fat. The evidence for this opinion was sketchy. A flood of other papers has followed, and in the past year there have come to my attention one by Shepardson,[54] one by Nahum and Himwich [55] and one from Ann Arbor by a pupil of Newburgh, Freyberg.[56] In Shepardson's 17 cases the dosage varied from 20 to 64 units daily. The quantity was increased

50. Pitfield, R. L.: Insulin in Infantile Inanition, New York M. J. **118**:217 (Aug. 15) 1923.

51. Marriott, W. McK.: The Food Requirements of Malnourished Infants with a Note on the Use of Insulin, J. A. M. A. **83**:600 (Aug. 23) 1924.

52. Barbour, Orville: The Use of Insulin in Undernourished Non-Diabetic Children, Arch. Pediat. **41**:707 (Oct.) 1924.

53. Falta, W.: Ueber Mastkuren mit Insulin und über insuläre Fettsucht, Wien. klin. Wchnschr. **38**:757 (July 2) 1925.

54. Shepardson, H. C.: Insulin Fattening in Ambulatory Patient, California & West. Med. **40**:14 (Jan.) 1934.

55. Nahum, L. H., and Himwich, H. E.: Insulin and Appetite: I. A Method for Increasing Weight in Thin Patients, Am. J. M. Sc. **183**:608 (May) 1932.

56. Freyberg, R. H.: A Study of the Value of Insulin in Undernutrition, Am. J. M. Sc. **190**:28 (July) 1935.

to a point at which physiologic effects were manifest, but because of a variation in tolerance adequate doses were approached cautiously. The results were almost uniformly favorable. There were two types of increase in weight. In one group the gain was rapid and fairly continuous; in the other the gain was rapid at the beginning but became less marked with time and finally stopped, whether or not more insulin was given. A general improvement also was noticed, attributed to a tonic effect. Nahum comments on the feeling of pleasure in eating that appears. One of his patients, who was nauseated by the sight of food before treatment, developed a ravenous appetite and ate with satisfaction. He suggests that in persons with anorexia an actual inhibition of the secretion of insulin is mediated through the hypothalamus, accounting for the anorexia. Freyberg, on the other hand, expresses doubt, basing this on a careful study of 9 thin patients, who were treated without knowing that they were receiving insulin or that an increase in appetite or hunger was expected. The length of time that insulin was administered was from eight to forty-five days. The dose of insulin at the time the injections were stopped varied from 18 to 60 units; hypoglycemic reactions occurred on from one to three occasions in 4 patients. Only 2 patients had improved appetites, and only these 2 ate more during the course of treatment than before. They alone gained weight, and they had been gaining nearly as fast before. In another experiment, with 11 patients, Freyberg tested and compared the effect of a high caloric diet alone, the additional effect of a placebo and the additional effect of insulin. Good results were obtained in only 3 patients in the group receiving insulin, whereas with the placebo 4 patients had good, and 3 slight, benefit. This investigation suggests that the benefit from insulin in cases of thinness is not attributable to the insulin. However, psychic therapy is not undesirable in cases of anorexia nervosa, and experience shows that the prescription of insulin, with its attending threat of hypoglycemic reaction, is a very effective placebo.

DIABETES INSIPIDUS

The value of injection of solution of posterior pituitary in controlling the symptoms of diabetes insipidus was demonstrated independently in 1913 by Farini and Ceccaroni [57] and by von den Velden.[58] The results are satisfactory in most cases, but such treatment has the disadvantage of provoking extremely disagreeable side-effects, such as pallor, headache, palpitation and diarrhea. These disadvantages are avoided by spraying

57. Farini, A., and Ceccaroni, B.: Influenza degli estratti ipofisari sull' eliminazione dell' acido ippurico, Gazz. d. osp. **34**:879, 1913.

58. von den Velden, R.: Die Nierenwirkung von Hypophysenextrakten beim Menschen, Berl. klin. Wchnschr. **50**:2083 (Nov.) 1913.

the substance into the nose or by applying it on cotton pledgets, as suggested by Blumgart;[59] unfortunately this is not always efficacious, and it is expensive. The administration of dry, powdered substance of the posterior lobe apparently is efficacious, more convenient and much less expensive. It was first suggested by André and Lucie Choay[60] in 1924 and later has been reported on favorably by Rosenberg,[61] Vidgoff,[62] Smith,[63] Canelo and Lisser,[64] Mainzer[65] and Adlersberg.[66] The economy is emphasized by Canelo and Lisser,[64] who treated a patient and noted that he required 1 cc. of solution of posterior pituitary twice daily, whether administered hypodermically or in a spray, at a cost of from $13 to $15 a month, whereas a month's supply of material to be snuffed, consisting of one hundred and twenty measured ¼ grain (0.016 Gm.) doses of posterior pituitary substance, cost only $4 a month, a significant saving of about $100 a year for "an equally efficient form of therapy." Each dose is weighed out and dispensed by the pharmacist in a "powder paper." When it is time for his medicine the patient unfolds the paper, rolls it up like a straw, inserts one end into the nostril and sniffs the powder. Four doses a day are required.

Mainzer describes 7 cases in which the nasal administration of powdered posterior pituitary substance controlled the thirst and polyuria of patients with normal neurologic and ophthalmic findings. He observed, as others have, that persons with diabetes insipidus secondary to encephalitis, basilary syphilitic meningitis and tumor are relatively insensitive to pituitary medication in any form. The feeling of thirst of Mainzer's patients disappeared in ten minutes. The diminution of

59. Blumgart, H. L.: The Antidiuretic Effect of Pituitary Extract Applied Intranasally in a Case of Diabetes Insipidus, Arch. Int. Med. **29**:508 (April) 1922.

60. Choay, André, and Choay, Lucie: Traitement du diabète insipide par des inhalations d'extrait de lobe posterieur d'hypophyse, Rev. neurol. **1**:267 (Feb.) 1924.

61. Rosenberg, Max: Zur Schnupfpulver-Therapie des Diabetes insipidus mit verschiedenen Hypophysen-Hinterlappen-Präparaten, Klin. Wchnschr. **9**:152 (Jan. 25) 1930.

62. Vidgoff, Ben: Posterior Pituitary Therapy in Diabetes Insipidus, Endocrinology **16**:289 (May-June) 1932.

63. Smith, F. M.: Diabetes Insipidus: Treatment by Intranasal Insufflation of Posterior Lobe Pituitary Powder, J. A. M. A. **102**:660 (March 3) 1934.

64. Canelo, C. K., and Lisser, H.: A Case of Diabetes Insipidus Controlled with Powdered Pituitary Posterior Lobe Extract Applied Intranasally, as Snuff, California & West. Med. **42**:178 (March) 1935.

65. Mainzer, Fritz: Ueber Fragen der Hypophysenhinterlappentherapie des Diabetes insipidus, Wien. Arch. f. inn. Med. **26**:101, 1934.

66. Adlersberg, D.: Dauertherapie des Diabetes insipidus, Ztschr. f. klin. Med. **128**:598 (Sept.) 1935.

diuresis lasted from eight to ten hours. As continued treatment led to compensation, there was considerable loss of weight, suspension of treatment being followed by a gain of weight up to 5 Kg. This observation is in conflict with the theory which regards the thirst of patients with diabetes insipidus as due to dehydration. In some cases an increased tolerance for water followed treatment, analogous to the increased tolerance for sugar in persons with diabetes mellitus after treatment with insulin; that is, after a time smaller amounts of the nasal powder sufficed to control the symptoms. The powder was diluted with lactose. There is no need for this; the undiluted powder is nonirritating.

Adlersberg [66] describes the cases of 2 patients treated effectively with powdered posterior pituitary substance for seven years, with no ill effects. The disturbance of water balance remained unaltered. Other medication is of little benefit in cases of diabetes insipidus. The estrogenic hormone appeared to be beneficial in a case reported by Troisier,[67] but it was without effect on 2 patients studied by Adlersberg. The administration of mercurial diuretics, aminopyrine and ergotamine, as well as the restriction of salt, is considered to be much less effective than treatment with solution of posterior pituitary or posterior pituitary powder; nevertheless it is of some usefulness in patients resistant to preparations of posterior pituitary.

A study of the composition of the blood and its variation under diverse influences, such as thirsting, restriction of salt and treatment with pituitary substance, is the subject of reports by Decourt and his associates.[68] The thirst in persons with diabetes insipidus, he concludes, is not related to the high values for chloride observed both in the plasma and in the corpuscles in the blood but is rather due to a diminished content of water, namely, a loss of the hydrophilia of the colloids of the tissues.

An interesting report based on the pathogenesis of diabetes insipidus is that of Biggart.[69] The theories of diabetes insipidus are reviewed. The current theory is based on the observations of Aschner [70] and of

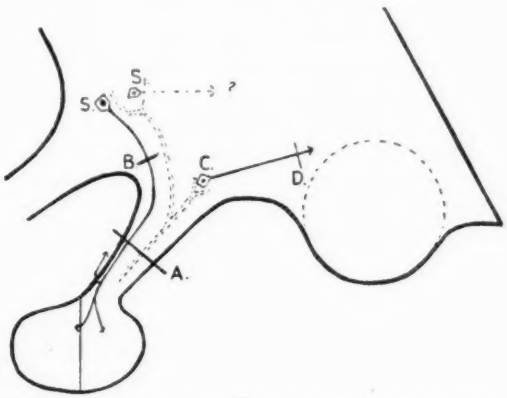
67. Troisier, Jean: Action antipolyurique des hautes doses de folliculine dans le diabète insipide de l'homme, Bull. et mém. Soc. méd. d. hôp. de Paris **48**:1451 (Nov. 18) 1932.

68. Decourt, J.: Diabète insipide: Etude de la composition du sang et de ses variations sous diverses influences (régime déchloruré, traitement hypophysaire, épreuve de la soif), Bull. et mém. Soc. méd. d. hôp. de Paris **51**:468 (March 25) 1935. Decourt, J.; Meyer, L.; Audry, M., and Lesourd, R.: Diabète insipide: Action du régime déchloruré sur la polyurie: Considérations sur l'élimination des chlorures, ibid. **50**:1695 (Dec. 24) 1934.

69. Biggart, J. H.: Diabetes Insipidus, Brain **58**:86 (March) 1935.

70. Quoted by Bailey and Bremer.[71]

Camus and Roussy,[70] who showed that hypophysectomy in itself did not produce polyuria but that examination of those animals in which the syndrome developed always revealed a lesion in the floor of the third ventricle. This view was confirmed by Leschke,[70] Houssay [70] and Bailey and Bremer,[71] who observed that injury of the infundibulotuberal region of the hypothalamus produced polyuria. It is also confirmed by Richter,[72] who has succeeded in producing permanent polyuria in cats by means of experimental lesions accurately placed in the region of the chiasm. The occurrence of diabetes insipidus in association with epidemic encephalitis, whether during the acute phase or as a sequel, has further emphasized the importance of the hypothalamus in the pathogenesis of the disease.



A diagram to illustrate the sites of the lesions producing diabetes insipidus. *S* indicates the nucleus supra-opticus; S_1, the tract described by Greving; *C*, the position of the tuberal nuclei; *C-D*, the descending tuberal tract, and *A*, *B*, *C*, *D*, possible sites of injury (after Biggart [69]).

Biggart describes 3 cases of diabetes insipidus to illustrate how lesions affecting different regions of the hypothalamus produce the disease and to explain why extracts of the posterior lobe of the pituitary gland are active in controlling the disease in some cases and not in others (figure). He says:

A lesion at "A" may produce a polyuria by interruption of the supra-optic-hypophyseal tract. This division would presumably lead to a diminution of the

71. Bailey, Percival, and Bremer, Frédéric: Experimental Diabetes Insipidus, Arch. Int. Med. **28**:773 (Dec.) 1921.

72. Richter, C. P.: Experimental Diabetes Insipidus, Brain **53**:76 (April) 1930.

secretion of the antidiuretic factor, but this would be compensated for by the pars tuberalis which escapes. In fact according to Rubio the pars tuberalis will hypertrophy. A lesion at "B" will cut off the secretory fibers to the whole epithelial investment of the pars nervosa and pars tuberalis [of the pituitary], and so lead to the establishment of a permanent diabetes insipidus. Such a case, however, will be controllable by injections of pituitrin as the effector pathway from the nuclei of the tuber cinerium is still intact. . . . A lesion at "C" or "D," however, which destroys the effector pathway, will result in a polyuria which is refractory to treatment. According to Dreyfus, such cases are rare in human pathology, and constitute but 5 per cent of all cases of diabetes insipidus.

Other writers place the percentage of these refractory cases at a higher figure. Cases of basal meningitis, syphilitic or otherwise, fall in the category.

A rôle in the pathogenesis of diabetes insipidus is attributed to the anterior lobe of the pituitary gland by Richter.[73] Total and partial hypophysectomy was performed on rats by a technic modified from that of Smith [74] and described in an earlier paper. The results were as follows: Total removal of the gland produced temporary diabetes insipidus in only twenty-eight of thirty-four animals and permanent diabetes in none. On the other hand, when the posterior lobe was removed entirely but a part of the anterior lobe was left, the diabetes in all the twenty-six animals proved permanent. These observations confirm the findings of von Hann [74] made in 1918 in a study of records made at autopsy on patients with diabetes insipidus. He noted that 20 patients suffering from this illness had lesions of the posterior lobe of the pituitary, with parts of the anterior lobe still intact, while 9 patients with much the same lesion but with the anterior lobe gone showed no diabetes insipidus. The experimental observations of Richter have been confirmed in Herbert Evans' laboratory by Pencharz, Hopper and Rynearson.[75] Their significance as yet is not entirely clear. The suggestion is made that the anterior lobe is responsible for a hormone with an action antagonistic to posterior pituitary.

II. NUTRITION

By Dr. Wilbur

Since the advent of the "vitamin era" greater interest has been shown by the people of civilized countries in the quality and kind of their food than in its quantity. Such a change in thought may prove to be one of the greatest public health movements of history if one can translate

73. Richter, C. P.: Experimental Diabetes Insipidus: Its Relation to the Anterior and Posterior Lobes of the Hypophysis, Am. J. Physiol. **110**:439 (Dec.) 1934.

74. Quoted by Richter.

75. Rynearson, E. H.: Personal communication to the author.

the results of experiments on the nutrition of animals in terms of nutrition of man and if the present economic depression is not too prolonged. McLester [76] well summarized this in his address entitled "Nutrition and the Future of Man," pointing to the tremendous influence of ridiculously small amounts of food and the influence man may have on his own destiny by taking them into consideration. During the period of twenty years from 1906 to the present, under conditions that were not varied except for improvement in ration, the normal standard rate of growth of the albino rat has trebled and the standard weight for the species has doubled. This improvement apparently has included all phases of physical development. Evidence also has been presented by McLester to demonstrate the improved physical condition and increased growth of Oriental and European immigrants to countries where life under improved nutritional conditions is possible. Studies in certain schools and universities in the United States and in England demonstrated an increase in the physical height of students over that of students of a generation ago. That increased physical efficiency may occur along with increased physical stature is indicated by studies in English schools and in the English flying corps. While the advantages of increased rate of growth are still debated, most physiologists apparently feel that the results are wholly favorable. While the potentialities of the human race for increases in longevity and improvement in vitality and vigor cannot be estimated, it must be admitted that they are great under circumstances of ideal conditions of nutrition.

The recent economic depression has affected the available supplies of food for the people of many countries throughout the world. Interest is focused again, as it was during the World War, on the problems of what constitutes undernutrition and adequate nutrition and how the latter may best be obtained for those who are in unfortunate economic circumstances. During the past year there have been interesting contributions to the problem of what constitutes malnutrition or undernutrition. Apparently, the old standard of body weight (of a child) compared with a table of standards in which the height may or may not be taken into consideration must be considered inadequate in terms of modern conceptions of nutrition. Even such studies as those made to differentiate the desirable weight ratios for children of various types of habitus through recognition that the size of the skeleton will determine the amount of soft tissues appropriate for an individual child, as noted by Boyd,[77] while an advance over older methods, must still be con-

76. McLester, J. S.: Nutrition and the Future of Man, J. A. M. A. **104**:2144 (June 15) 1935.

77. Boyd, J. D.: Normal Nutrition During Childhood: Critical Review, J. Pediat. **6**:249 (Feb.) 1935.

sidered inadequate. In fact, it is questionable whether physical measurements will prove adequate criteria in the determination of the nutritional state of the individual subject. An interesting presentation of this subject was a discussion on the assessment of the state of nutrition [78] held before the Section of Epidemiology and State Medicine of the Royal Society of Medicine. It was pointed out that one of the main reasons for the present confusion is oversight of the fact that the state of nutrition is dynamic and not static. Account must be taken of the fact that the state of nutrition of the individual subject in large part is a resultant of physiologic processes and therefore that a wide range of adaptability to varying circumstances is possible. "Primary" malnutrition, which is the result of dietary deficiency, must be contrasted with "secondary" malnutrition, attributable to other causes, such as disease of the gastro-intestinal tract or other organs. There are at present no sufficient physiologic criteria of adequacy of nutrition in many of its aspects. Consequently, there is little wonder that so much variability exists in studies of the incidence of malnutrition. At present one must be content perhaps with such anatomic standards as the height and weight and with such physiologic measures as the turgor of the tissues, color of the skin and mucous membranes, degree of alertness, evidence of apathy or irritability, poor posture, restlessness, disturbed sleep and signs of fatigue,[79] as well as with clinical estimates of the state of nutrition made by experienced physicians.

In any discussion of malnutrition the studies of Strang and his associates [80] are of interest, for these investigators have evidence to indicate that the gastro-intestinal tracts of undernourished subjects are not inferior to those of normal persons and that the undernutrition of such persons is not the result of anomalies of metabolism. The rôle of diseases of the gastro-intestinal tract in interfering with adequate nutrition or, as it is sometimes called, in conditioning states of deficiency is being repeatedly emphasized as an important cause of such states of deficiency in the United States.

The influence of the recent economic depression in the nutritional state of the people in this and other countries probably will not be known for many years. One reason for this is the lack of suitable criteria of malnutrition, and another is that a generation in the life of man covers many years. A recent League of Nations Bulletin, "Nutrition and

78. Magee, H. E., and others: Discussion on the Assessment of State of Nutrition, Proc. Roy. Soc. Med. **28**:713 (April) 1935.

79. Crawford, W. L.: Physical Examination of the Child: Its Objects and Methods, Illinois M. J. **65**:49 (Jan.) 1934.

80. Strang, J. M., and Evans, F. A.: Undernutrition and Its Treatment by Adequate Diet, Ann. Int. Med. **7**:45 (July) 1933.

Public Health,"[81] suggests that no country can claim that its population is satisfactorily fed. Poverty is mainly to blame, ignorance to a less extent. Significant in this respect is the fact that protective foods, richest in vitamins and minerals, are the most expensive and in all countries are beyond the means of the great masses of people. Burnet and Aykroyd, who made the report, allege that in Great Britain between 10 and 25 per cent of the population cannot afford a diet of the type and quality now known to be essential as a safeguard against malnutrition and disease. It is claimed that more than 22 per cent of children in the United States investigated up to 1924 showed symptoms of malnutrition. In answer, the chief medical officer of the ministry of health of Great Britain has stated that the nutrition of the people of his country is better than at any period of which there is record.

In a recent summary on the nutritional status of 4,500 children who were on relief in San Francisco, Geiger and Barrett[82] conclude that even on conservative interpretation of their observations it must be admitted that the nutritional status of children who have been on commissary relief compares favorably with that of a normal or even a more privileged group in the community. In the establishment of relief rations considerable attention must be paid to a variety of factors emphasized in an editorial comment in *The Journal of the American Medical Association.*[83] These include racial differences as well as national habits in relationship to the consumption of food and the lack of safety in trusting the individual to the guidance of his appetite alone in the selection of an adequate diet. A practical fact in regard to the diet of persons on relief is that mentioned by Sherman,[84] who pointed out that nutritional benefit comes from what one eats more than from lists of what one should eat.

VITAMINS

Interest in the vitamins in the past year has been directed principally toward their further chemical identification, their synthesis and the preparation of concentrates and crystals suitable for oral and parenteral administration. Progress has been made, also, in the direction of the relation of vitamins to infections and in studies of the quantitative requirements for some of the vitamins and their metabolic activity in the animal organism.

81. Nutrition and Public Health, London letter, J. A. M. A. **105**:728 (Aug. 31) 1935.

82. Geiger, J. C., and Barrett, P. S.: Nutritional Survey of Four Thousand Five Hundred Children on Relief, Am. J. Pub. Health **25**:183 (Feb.) 1935.

83. Diet and Relief, editorial, J. A. M. A. **104**:320 (Jan. 26) 1935.

84. Sherman, H. C.: Food and Health, New York, The Macmillan Company, 1934, p. 99.

Vitamin A.—It seems clear that vitamin A is closely related to the yellow pigment carotene. Vitamin A is the primary alcoholic derivative produced by the symmetrical division into two parts of the beta-carotene molecule. Beta-carotene consists of two B ionone rings united by a series of conjugated double bonds. Attempts to synthesize vitamin A have been made but have proved unsuccessful. For purposes of administration, livers of fish, particularly of the halibut, act as the richest known source of this vitamin. Concentrates and crystalline forms of the vitamin have not been produced. The feeding of vitamin A is superior to the administration of carotene because the former is more rapidly absorbed, and in the presence of fever or diarrhea carotene is poorly absorbed.

The quantitative requirement of vitamin A is unknown. However, it is estimated by Salter [85] that the minimal average value expressed as carotene is 0.3 mg. daily. The difficulty in expressing in exact figures the requirement of any vitamin is realized when one considers the influences of absorption, storage and destruction and the variability in minimal and optimal levels of requirement.

Among the interesting studies of metabolism of vitamin A recently reported is that of Baumann, Riising and Steenbock.[86] These workers demonstrated that 95 per cent of vitamin A in the organism is stored in the liver and the remainder in the kidneys and lungs. Apparently 20 per cent of ingested vitamin is stored in the liver. The speed of absorption is surprisingly great, for from three to six hours after administration the larger part of the assimilated vitamin is already stored in the liver. Most of the ingested vitamin is destroyed or inactivated in the bowel. It is also pointed out that it is easier to maintain than to replenish stores of vitamin A. In contrast with these findings, Drummond, Bell and Palmer [87] report almost complete absorption of vitamin A by a patient whose condition led to part of the content of the thoracic duct being diverted into the pleural cavities. It is of interest to note that the absorption of vitamin A in this case was much more satisfactory than that of carotene; this bears out previous experimental evidence. Both carotene and vitamin A appear to be present (in the chylous fluid) in colloidal form and closely associated with the highly dispersed fat.

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85. Salter, W. T.: Quantitative Aspects of Vitamin Requirement, J. Am. Dietet. A. **10**:296 (Nov.) 1934.

86. Baumann, C. A.; Riising, Blanche M., and Steenbock, H.: Fat-Soluble Vitamins: XLII. The Absorption and Storage of A in the Rat, J. Biol. Chem. **107**:705 (Dec.) 1934.

87. Drummond, J. C.; Bell, Muriel E., and Palmer, Elizabeth T.: Observations on the Absorption of Carotene and Vitamin A, Brit. M. J. **1**:1208 (June 15) 1935.

In studies on the carotene and vitamin A content of the blood serum of man, Schneider and Widmann [88] have observed that these substances are present only in the serum and not in the corpuscles. The effect of age is interesting, since it was noted that with increasing age the carotene content of the serum increases, while the vitamin A content decreases. Some evidence of the situation of storage of vitamin A in the liver is presented by Lasch,[89] who has demonstrated that in experimental animals (rats and rabbits) fatal phosphorus poisoning does not alter the amount of vitamin A stored in the liver; this suggests that storage occurs principally in the reticulo-endothelial cells. The Kupffer cells are not apparently affected following the administration of phosphorus, whereas the hepatic parenchymal cells are badly damaged. The possibility that vitamin A activity may influence the metabolism of cholesterol as a result of its action on the liver is suggested by Lasch.[90] He noted an increase in the cholesterol of the serum after the administration of large doses of vitamin A. The elevation of the cholesterol content is attributable primarily to an increase of the cholesterol esters fraction, and this indicates, according to Lasch, a direct action on the regulatory function exerted by the liver on the metabolism of cholesterol.

The clinical and pathologic features of avitaminosis caused by a lack of vitamin A have been described on numerous occasions. A splendid review of this subject has been made by Sweet and K'ang,[91] who have had unusually large experience among the Chinese. The effects of deficiency of vitamin A on the gastro-intestinal tract are rarely emphasized. It is of interest to note that Richards [92] observed that the earliest macroscopic sign of lack of vitamin A in young rats is in the epithelial lining of the digestive tract. Inflammation of the duodenum, small intestines and cecum is frequent, and in the glandular portion of the stomach there may be pittings, hemorrhagic points and even ulceration.

Whether or not the effects of avitaminosis may persist over a long period despite a subsequent liberal intake of the vitamin is a matter of great practical importance. From his experimental studies Richards produces evidence that pathologic conditions attributable to deficiency

88. Schneider, E., and Widmann, F.: Carotene and Vitamin A Contents of Human Serum, Klin. Wchnschr. **14**:670 (May 11) 1935.

89. Lasch, Fritz: Vitamin A Metabolism and Liver in Experimental Phosphorus Intoxication, Klin. Wchnschr. **14**:1070 (July 27) 1935.

90. Lasch, Fritz: Action of Vitamin A on Serum Cholesterol of Human Subject, Klin. Wchnschr. **13**:1534 (Oct. 27) 1934.

91. Sweet, L. K., and K'ang, H. J.: Clinical and Anatomic Study of Avitaminosis A Among the Chinese, Am. J. Dis. Child. **50**:699 (Sept.) 1935.

92. Richards, Marion B.: The Rôle of Vitamin A in Nutrition, Brit. M. J. **1**:99 (Jan. 19) 1935.

of vitamin A may persist several months after a normal diet has been resumed. The author comes to the conclusion, difficult of proof, that damage caused by insufficiency of vitamin A in early youth cannot afterward be made good by an adequate supply of the vitamin, and chronic ill health may result.

Perhaps the most interesting clinical problem relative to vitamin A is that in regard to its relation to renal lithiasis. It has been recognized for several years that in the albino rat on a diet deficient in vitamin A there develops keratinization of the epithelium of the renal pelvis, and frequently urinary calculi of the calcium phosphate type occur. The application of this knowledge to renal lithiasis of man has provoked a variety of comment. Joly [93] expresses the opinion that the hypothesis that the presence of stones is evidence of a deficiency disease (principally, if not exclusively, attributable to deficiency of vitamin A) is the most plausible and probable that as yet has been advanced. One of the chief exponents of this theory, Higgins,[94] offers evidence that the addition of vitamin A causes disintegration and solution of the calculi experimentally produced in rats, and he adds that an acid ash diet high in vitamins has produced a decrease in size or total disappearance of renal calculi of some patients. The opinion of many urologists is apparently similar to that of Keyser,[95] who holds that a general survey of the subject reveals points which cannot be reconciled with certain clinical facts. Final conclusions must await further clinical study concerning this interesting problem. A good summary of it is to be found in a recent report of the Council on Pharmacy and Chemistry of the American Medical Association.[96]

The relation of vitamin A to resistance to infection will be considered subsequently.

The Vitamin B Complex.—Vitamin B_1: Interest in vitamin B_1 has been concerned principally with the isolation of the vitamin in crystalline form, studies of its chemical composition and preparation of concentrates. In the past few years crystals with vitamin B_1 activity have been prepared by Kinnersley and his associates [97] in England, Williams [98] in

93. Joly, J. S.: The Etiology of Stone, J. Urol. **32**:541 (Dec.) 1934.

94. Higgins, C. C.: Production and Solution of Urinary Calculi, J. A. M. A. **104**:1296 (April 13) 1935.

95. Keyser, L. D.: Recurrent Urolithiasis: Etiologic Factors and Clinical Management, J. A. M. A. **104**:1299 (April 13) 1935.

96. Vitamin A and Urinary Lithiasis, report of the Council on Pharmacy and Chemistry, J. A. M. A. **105**:1983 (Dec. 14) 1935.

97. Kinnersley, H. W.; O'Brien, J. R., and Peters, R. A.: LXXXI. Crystalline Vitamin B_1, Biochem. J. **29**:701 (March) 1935.

98. Williams, R. R.: The Structure of Vitamin B, J. Am. Chem. Soc. **57**:229 (Jan.) 1935.

America, Windaus, Tschesche and Ruhkopf [99] in Germany and Van Veen [100] in Batavia. Recent cooperative efforts lead one to the conclusion that there is no reason for questioning the view that vitamin B_1 has been isolated, although certain details have yet to be settled. The exact chemical structure has not been clearly established, but the vitamin consists of a single molecule, with a formula of $C_{12}H_{18}O_2N_4S$. Fortunately, the wide distribution of vitamin B_1 affords a ready supply; synthesis, which will be a difficult task according to Kendall,[101] is not necessary in order to provide an available source of its concentrates and crystals. The vitamin in crystalline form may be purchased on the market at the present time.

There has been no significant advance in the knowledge of the physiologic activity of vitamin B_1; it appears to have the property of a co-enzyme-like substance intervening in the chain of reactions in the oxidation of carbohydrate. Studies of the vitamin B content of various organs in the experimental animal are of interest. Brodie and MacLeod [102] noted that the liver of the rat which was on a normal diet contained ten times as much vitamin B per gram of tissue as muscle contained. The kidney contained a half and the brain a third as much as did the liver. While the heart muscle contained a quantity equal to that of the liver, the blood, the spleen and the lung contained traces only.

Cowgill [103] has published a summary in monograph form of his extensive studies on the vitamin B requirement of man, in which he summarizes the three important variables determining the requirement of vitamin B, namely, (1) body weight, (2) total metabolism or calories and (3) maximal normal weight of the species. He presents a formula which is applicable in determining the vitamin B requirement of man. Salter suggests that the vitamin B requirement of man is probably 0.5 mg. daily. This is a low estimate compared to that of Cowgill [103] and of Vorhaus, Williams and Waterman.[104]

Beriberi is recognized rarely in the United States, but whether less severe states of deficiency of vitamin B are common is a matter for

99. Windaus, Tschesche and Ruhkopf, quoted by Kinnersley, O'Brien and Peters.[97]

100. Van Veen, quoted by Kinnersley, O'Brien and Peters.[97]

101. Kendall, E. C.: Vitamins from a Chemical Viewpoint, M. Clin. North America **19**:477 (Sept.) 1935.

102. Brodie, Jessie B., and MacLeod, Florence L.: Quantitative Experiments on the Occurrence of Vitamin B in Organs, J. Nutrition **10**:179 (Aug.) 1935.

103. Cowgill, G. R.: The Vitamin B Requirement of Man, New Haven, Conn., Yale University Press, 1934.

104. Vorhaus, M. G.; Williams, R. R., and Waterman, R. E.: Studies on Crystalline Vitamin B_1, J. A. M. A. **105**:1580 (Nov. 16) 1935.

debate. Recent studies of Vorhaus, Williams and Waterman are interesting in this respect, since these investigators had available for therapeutic use a crystalline preparation of vitamin B_1. They estimate the normal intake of B_1 for adult man to be 1 mg. daily and express the opinion that the minimal therapeutic dose that can be relied on to abolish any accumulated deficit is 10 mg. daily. Studies of patients with diabetes to whom the crystalline product was administered indicated an increase in the tolerance for carbohydrate of just over 50 per cent of the patients. Good results in the treatment of patients with a variety of forms of polyneuritis were observed, and the amelioration of associated symptoms, such as weakness, loss of appetite and paresthesia, far exceeded the relief of pain. In a selected group of patients who had hypotonicity of the gastro-intestinal tract without apparent organic cause but who had associated anorexia, constipation and vague muscular pains, much symptomatic relief was obtained. As a result of these studies, Vorhaus and his associates are inclined to believe that states of deficiency of vitamin B are far more frequent than previously has been thought.

Elsom [105] has reported interesting studies of 2 patients with deficiency of vitamin B: To one, for five months a diet was given which was moderately deficient in vitamin B, although adequate in every other known requirement; the other patient had beriberi. While marked relief of some symptoms was obtained after the addition of vitamin B_1 and B_2, residual symptoms, finally relieved by the administration of yeast, suggest that there are in the vitamin B complex factors of significance other than B_1 and B_2. The principal effects of the absence of vitamin B seemed to be on the gastro-intestinal tract and the nervous system. Edema and macrocytic anemia may also occur, and secondary effects on the circulatory system are not uncommon.

Strauss [106] has reemphasized the importance of nutritional factors in the so-called "alcoholic" polyneuritis. He noted improvement of all of the 10 patients who had this disease when they continued to take their customary amount of alcohol but also received diets high in vitamin content, with yeast or yeast products by mouth and vitamin B concentrates and liver extract parenterally.

The use of concentrates of vitamin B_1 and the use of crystalline vitamin B_1 in cases of diabetes is considered in the section on metabolism.

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105. Elsom, Katharine O.: Experimental Study of Clinical Vitamin B Deficiency, J. Clin. Investigation **14**:40 (Jan.) 1935.

106. Strauss, M. B.: The Etiology of "Alcoholic" Polyneuritis, Am. J. M. Sc. **189**:378 (March) 1935.

Vitamin B_3: Further evidence of the existence of Vitamin B_3 is presented by Waterman and Ammerman.[107] The clinical significance of this apparent fraction of the vitamin B complex is unknown.

Vitamin B_4: György [108] reports that in the absence of this fraction there occur lesions of the nervous system, with disturbances in coordination and ataxia.

Vitamin B_6: This subject is considered in the section on vitamin G.

Vitamin C.—Since the chemical identity of vitamin C has been established, interest in this vitamin has been directed principally toward studies of the metabolism of this substance in the animal organism and the effects of its administration in crystalline form.

One of the most interesting phases of vitamin requirement is that which has to do with the levels of minimal and optimal intake and utilization. King and Menten [109] have demonstrated the significance of this phenomenon in work with guinea-pigs fed vitamin C in abundant protective and subprotective quantities. In animals with partial depletion without external signs of scurvy the time of survival was shortened about 50 per cent and loss of weight was severe. King and Menten demonstrated that there is a wide zone of deficiency in vitamin C without the appearance of scurvy, wherein physiologic processes are subnormal and sensitivity of the animal to injury from bacterial toxins is increased. Jungeblut and Zwemer [110] present evidence that diphtheria toxin is inactivated by vitamin C in vitro. These and other works suggest a relationship between cevitamic acid and the process of immunity.

Interest in the clinical significance of vitamin C has been increased in recent years because of the suggestion by Rinehart and his associates [111] that vitamin C is a specific etiologic factor in rheumatic fever. Perry [112]

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107. Waterman, R. E., and Ammerman, M.: Studies of Crystalline Vitamin B: Effect of Graduated Doses on Pigeons, J. Nutrition **10**:161 (Aug.) 1935.

108. György, Paul: LXXXVI: Investigations on the Vitamin B_2 Complex: I. The Differentiation of Lactoflavin and the "Rat Antipellagra" Factor, Biochem. J. **29**:741 (March) 1935.

109. King, C. G., and Menten, M. L.: Influence of Vitamin C Level upon Resistance to Diphtheria Toxin, Changes in Body Weight and Duration of Life, J. Nutrition **10**:129 (Aug.) 1935.

110. Jungeblut, C. W., and Zwemer, R. L.: Inactivation of Diphtheria Toxin in Vivo and in Vitro by Crystalline Vitamin C (Ascorbic Acid), Proc. Soc. Exper. Biol. & Med. **32**:1229 (May) 1935.

111. Rinehart, J. F.; Conner, C. L., and Mettier, S. R.: Further Observations on Pathologic Similarities Between Experimental Scurvy Combined with Infection and Rheumatic Fever, J. Exper. Med. **59**:97 (Jan.) 1934.

112. Perry, C. B.: Rheumatic Heart Disease and Vitamin C, Lancet **2**:426 (Aug. 24) 1935.

and Faulkner,[113] as well as others, disagree with this conclusion. While both of the latter observers could find evidence suggesting mild degrees of deficiency of vitamin C in some cases, they did not believe it to be a significant factor, and in the experience of Faulkner the administration of vitamin C to patients who had rheumatic fever did not influence the course of the disease.

A relationship between vitamin C and the blood was suggested in 1934 by Presnall,[114] who noted a reduced number of platelets and anemia in cases of deficiency of vitamin C. Minot [115] emphasizes the occurrence of a normocytic or slightly macrocytic anemia in persons with deficiency of vitamin C. Faulkner has noted a slight but definite reticulocyte response following the administration of large quantities of orange juice or crystalline vitamin C, roughly proportional to the severity of the infection presented by the patient.

The fundamental importance of vitamin C in the formation of normal intercellular substance has been demonstrated by Menkin and his associates.[116] The failure to form this substance with normal properties in the presence of deficiency of vitamin C may be the result of reduced cellular oxidation.

There has been much discussion in the past year about the validity of the test of capillary resistance as a measure of deficiency of vitamin C and consequently of the incidence of such deficiency. Dalldorf and Russell,[117] who advocated the use of the test, report further on their studies of the inmates of a county home. To 14 inmates, tests of whom indicated reduced capillary resistance, 100 mg. of cevitamic acid was given intravenously. All of them made a prompt and marked response in capillary resistance, and the increased resistance persisted for twenty-four hours. The observers suggest that the individual requirement of antiscorbutic foods may vary and that various persons may differ regarding the absorption and utilization of the vitamin. It seems reasonable to hope that in the future a more satisfactory method will be established as a measure of sufficiency of vitamin C. Such a method is desirable in

113. Faulkner, J. M.: The Effect of Administration of Vitamin C on the Reticulocytes in Certain Infectious Diseases: A Preliminary Report, New England J. Med. **213**:19 (July 4) 1935.

114. Presnall, A. K.: The Relation of Avitaminosis C to Blood Clotting, J. Nutrition **8**:69 (July) 1934.

115. Minot, G. R.: The Anemias of Nutritional Deficiency: Etiology, Diagnosis, Treatments and Prevention, J. A. M. A. **105**:1176 (Oct. 12) 1935.

116. Menkin, Valy; Wolbach, S. B., and Menkin, Miriam F.: Formation of Intercellular Substance by the Administration of Ascorbic Acid (Vitamin C) in Experimental Scorbutus, Am. J. Path. **10**:569 (Sept.) 1934.

117. Dalldorf, Gilbert, and Russell, Hollis: The Effect of Cevitamic Acid Injections on Capillary Resistance, J. A. M. A. **104**:1701 (May 11) 1935.

view of the variability of results with the test of capillary resistance. Perry suggests such a method, which might be called a test of vitamin C tolerance. A measured amount of the vitamin is given, and its excretion in the urine is studied. By a person well supplied with vitamin large quantities of the ingested vitamin will be excreted in the urine, in which it can be estimated quantitatively. On the other hand, if there is a deficiency of vitamin C, the organism will utilize much of the ingested vitamin and but small quantities will be excreted in the urine. Since the estimation of vitamin C in the urine is relatively simple, this method may become the most accurate measure in the clinical investigation of deficiency of vitamin C.

The use of crystalline cevitamic acid in the treatment of patients with infantile scurvy has proved effective, according to Abt and Epstein,[118] who noted that the blood of scorbutic infants was low in vitamin C. Treatment of hemorrhagic conditions with cevitamic acid has been suggested. The results seem variable. Junghans [119] expresses the opinion that it is of value in the treatment of uterine bleeding of various types. The mechanism of its activity is unknown, although it may effect changes in the intercellular substance of the capillaries.

A practical point in the intravenous administration of cevitamic acid is suggested by Anderson and Leake,[120] who noted that hemolysis of the erythrocytes may occur if the crystals are dissolved in distilled water. They recommend for intravenous use solutions of the sodium salt of cevitamic acid approaching approximate isotonicity; that is, 1 per cent of the salt dissolved in physiologic solution of sodium chloride or 3 per cent dissolved in distilled water. If only the acid is available, it should be neutralized with half its weight of sodium bicarbonate (sterile) in physiologic solution of sodium chloride or water before it is injected.

Vitamin G.—Ever since the demonstration that the original water-soluble vitamin B is composed of several separate fractions there has been much interest in the number, character and physiologic properties of the various components. A heat-stable, antidermatitic factor was called vitamin B_2 or G. One year ago it was stated in this review that vitamin G was chemically closely related to the pigment group of flavines. Since that time, work has appeared which suggests that vitamin G is in fact composed of two distinct constituents, one a flavine and the other a supplementary substance contained in yeast extract. The latter

118. Abt, A. F., and Epstein, I. M.: Cevitamic Acid (Ascorbic Acid) in the Treatment of Infantile Scurvy, J. A. M. A. **104**:634 (Feb. 23) 1935.

119. Junghans, E.: Vitamin C in Treatment of Gynecologic Hemorrhages, Klin. Wchnschr. **14**:899 (June 22) 1935.

120. Anderson, H. H., and Leake, C. D.: Hemolytic Action of Cevitamic (Ascorbic) Acid, J. A. M. A. **105**:1033 (Sept. 28) 1935.

appears identical with the "factor Y" of Chick, Copping and Edgar [121] and with György's vitamin B_6. György [122] points out that neither lactoflavine nor vitamin B_6 alone has growth-promoting action, but together they do have this action; apparently the pellagra-preventing factor corresponds to the supplementary substance, or vitamin B_6. György expresses the opinion that Castle's extrinsic factor will be more closely related to lactoflavine than to the pellagra-preventing, or vitamin B_6, factor. A distinct difference in the content of these two factors in certain foods is of further interest in showing their independent existence. György points out that fish muscle is a rich source of the antipellagra factor (B_6) but that it is practically devoid of lactoflavine, while egg, despite its high content of lactoflavine, is devoid of antipellagra activity. The chemical character of the B_6 fraction is unknown.

There is still much discussion concerning the etiology of pellagra. The importance of the so-called secondary pellagra, that is, pellagra occurring secondary to an initial gastro-intestinal disorder the causation of which is entirely unconnected with pellagra, is reemphasized by Simpson.[123]

Despite variability in opinion as to the etiology, the treatment of pellagra is chiefly dietary. The rapid strides which have been made in this respect are well illustrated by Spies [124] in his studies at the Lakeside Hospital in Cleveland. From 1926 to 1930, 54 per cent of 73 patients with pellagra died despite good hospital care. During the past five years Spies and his associates [124b] have been able to reduce the mortality in persons with severe pellagra to 5 per cent or less. For the treatment of early pellagra these observers suggest adequate rest, a diet of 4,000 calories or more daily, supplemented by from 10 to 20 Gm. of good brewer's yeast or wheat germ in iced milk or eggnog several times daily, so that the patient receives from 75 to 100 Gm. daily. If necessary, to this may be added parenteral injections of liver extract, from three to five doses of 20 cc. daily. Tincture of opium (from 2 to 5 or 6 cc. daily) may be used but it is not usually efficacious.

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121. Chick, Harriette; Copping, Alice M., and Edgar, Constance E.: LXXXIV. The Water-Soluble B-Vitamins: IV. The Components of Vitamin B_2, Biochem. J. **29**:722 (March) 1935.

122. György, Paul: LXXXVII. Investigations on the Vitamin B_2 Complex: II. The Distribution of Lactoflavin and of the "Pellagra-Preventing Factor" (Vitamin B_6) in Natural Products of Animal Origin, Biochem. J. **29**:760 (March) 1935.

123. Simpson, S. L.: Secondary Pellagra, Quart. J. Med. **4**:191 (April) 1935.

124. Spies, T. D.: (*a*) Medical Treatment of Pellagra, J. A. M. A. **104**:1377 (April 20) 1935; (*b*) Medical Treatment of Early Pellagra, ibid. **105**:1028 (Sept. 28) 1935.

The Occurrence of Other Essential Foodstuffs.—It is not clearly established that all possible essential foodstuffs have been recognized. In fact, each year there is reported the discovery of new essential substances not included in the present list of vitamins or minerals. Some of these substances have been called vitamins to establish their indispensable character. Two unsaturated fatty acids, linoleic and linolenic, which are nutritionally essential, have been named vitamin F. In the past year the existence of another essential foodstuff has been suggested by the work of Dam,[125] who describes a deficiency disease resembling scurvy in chicks, but it is not prevented by cevitamic acid. It is believed that the hemorrhagic tendency in this disease is produced by the absence of a fat-soluble substance which is antihemorrhagic, which is neither vitamin A nor vitamin D and which Dam has called the *Koagulations Vitamin,* vitamin K. Hog liver and hemp seed are said to be the best sources, while cod liver oil is practically devoid of the substance.

Vitamin Therapy.—The Council on Pharmacy and Chemistry of the American Medical Association[126] has published an interesting report, "Shotgun Vitamin Therapy," in which is pointed out the frequent lack of rationale in the use of many preparations now on the market which contain combinations of all or some of the vitamins, frequently combined with some mineral or minerals. The lack of necessity of administering such complex combinations for the maintenance of health when a well balanced diet is taken and the almost complete absence from the literature of evidence suggesting the value and safety of such preparations are emphasized. Until such evidence is presented, it seems safer to avoid the general use of such preparations.

A few studies have been made on the value of local applications of vitamins in promoting the healing of wounds. After examining the effect of such applications, Lauber[127] came to the conclusion that the local application of vitamin A produces no acceleration in the process of healing and may in fact retard it. The application of vitamins B and C seems to retard healing, whereas after the application of vitamin D in small doses there may be the slightest acceleration, and in large doses retardation, in healing. Although Lauber believes that the value of vitamin ointments is questionable, he found evidence that small doses of vitamin A given by mouth work most satisfactorily in accelerating healing of wounds.

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125. Dam, Henrik: CLIV. The Antihaemorrhagic Vitamin of the Chick, Biochem. J. **29**:1273 (June) 1935.

126. Shotgun Vitamin Therapy, report of the Council on Pharmacy and Chemistry, J. A. M. A. **105**:1037 (Sept. 28) 1935.

127. Lauber, H. J.: Experimental Studies on Relations Between Vitamins and Healing of Wounds, Beitr. z. klin. Chir. **151**:565 (June 5) 1935.

RELATION OF VITAMINS TO INFECTIONS

Perhaps nothing in regard to the vitamins engages the attention to such a degree as the so-called anti-infective power of certain vitamins. As previously emphasized, there is no evidence to suggest that vitamin A has any anti-infective power other than its ability to maintain in a good state the epithelial barriers of the organism. The crux of the situation will lie in the demonstration, or in the failure to demonstrate, that an amount of a vitamin in excess of that normally obtained by well nourished persons will further increase their resistance to infection. During the past year numerous papers have appeared supporting or denying the valuable effect of vitamin A in the treatment of the common cold and other infections. There is a suggestion in the work of Cameron [128] and of Shibley and Spies [129] that although excess quantities of vitamin A did not reduce the incidence of acute infection of the respiratory tract the average duration of such infections was somewhat reduced. In the observations reported by Cameron, carotene was apparently as effective as vitamin A.

Although vitamin A apparently lacks anti-infective power, except in maintaining a normal epithelial barrier, there is recent evidence to suggest that once the epithelial barrier of the organism has been overcome, vitamin C may increase the powers of resistance against infection.

The evidence produced by Jungblutt and Zwemer suggests that vitamin C bears a relationship to immunologic processes, since guinea-pigs well fortified with vitamin C were able to resist the effects of diphtheria toxin and in vitro diphtheria toxin was found to be inactivated by cevitamic acid. The clinical bearings of these observations are as yet uncertain. Although it is recognized that patients who have scurvy are more susceptible to infection than are normal persons, vitamin C has not been widely used as an anti-infective agent.

VITAMIN D, CALCIUM AND PHOSPHORUS

Any discussion of recent advances in the knowledge of one of these factors must take into account all of them. As Bills [130] has well expressed it:

> Confusion in this field is understandable when one contemplates the permutations and combinations which are possible in a system comprising several forms of calcium and phosphorus in the blood, a reservoir and depository of these

128. Cameron, Hazel C.: The Effect of Vitamin A upon Incidence and Severity of Colds Among Students, J. Am. Dietet. A. **11**:189 (Sept.) 1935.

129. Shibley, G. S., and Spies, T. D.: The Effect of Vitamin A on the Common Cold, J. A. M. A. **103**:2021 (Dec. 29) 1934.

130. Bills, C. E.: Physiology of the Sterols, Including Vitamin D, Physiol. Rev. **15**:1 (Jan.) 1935.

elements in bone, a fluctuating intake and output of them in the diet and excretions, and a dumping place for them in the soft tissues—all under the influence of many factors besides the parathyroid glands and the several forms of Vit. D. As for the hormones and the vitamin, which seem to be the major forces in the system, it is most satisfactory to regard them as acting together, complementing, supplementing, or opposing each other as the occasion demands.

Vitamin D.—Chemically, this vitamin is closely related to ergosterol, but as yet it is not known what structural changes occur when inactivated ergosterol is changed to the active form by irradiation. It seems widely accepted that vitamin D may exist in several different chemical forms, and there is evidence that provitamin D activity is not limited to ergosterol. The Kochs [131] have produced evidence, for example, that cholesterol itself, or a modification of it produced by heat, by alkali or by both, also has provitamin D potency. Although vitamin D is widely distributed throughout the animal kingdom, it is abundant only in fish, and except for occasional amounts gained by eating such foods as fish or eggs, the vitamin must normally be obtained by exposure of the surface of the body to the sun (Bills). Vitamin D may enter the circulation by several routes, and its absorption through the skin is well recognized. Although a considerable quantity of ingested vitamin D appears in the feces, it is not known whether this is the result of failure of absorption or whether it is the result of absorption with subsequent reexcretion.

Calcium and Phosphorus (Summarized from Schmidt and Greenberg [132]).—Animal organisms are dependent for their supply of these elements on plants, which in turn derive their needs from the soil or, in the case of aquatic plants, from the surrounding water. For man, the principal sources of these elements are milk and its products; nuts; certain vegetables, particularly beans; eggs; cereals, and meat. The form in which calcium and phosphorus exist is determined in part by the acid or alkaline reaction of the food, but inorganic salts, particularly calcium phosphate, are the principal sources of supply. The absorption of phosphorus, which always occurs in biologic material in the oxidized forms, namely, as derivatives of phosphoric acid, is delayed in the gastrointestinal tract, so that in all probability much of the calcium is absorbed before most of the phosphoric acid is set free by a process of hydrolytic cleavage. The advantage of this provision is that otherwise a considerable amount of calcium phosphate would be formed, and this,

131. Koch, Elizabeth, and Koch, F. C.: Fractionation Studies on Provitamin D, Science **82**:394 (Oct. 25) 1935.

132. Schmidt, C. L. A., and Greenberg, D. M.: Occurrence, Transport and Regulation of Calcium, Magnesium and Phosphorus in the Animal Organism, Physiol. Rev. **15**:297 (July) 1935.

having low solubility, probably would lead to decreased absorption of both elements.

In the absorption of calcium and phosphorus from the intestine, hydrochloric acid is an extremely important but not indispensable factor as an agent for effecting solution of insoluble calcium phosphate by the formation of more soluble chlorides of calcium. The small intestine, and particularly the duodenum, is important in the absorption of calcium salts.

The bulk of the calcium in the body exists in the skeleton, while phosphorus is present also widely distributed in the soft tissues and body fluids. Sherman [84] estimates that 1 Gm. of calcium a day would include an ample margin of safety for the average person, while an average intake of from 1 to 1.2 Gm. of phosphorus is a safe figure for the average man.

Calcium and phosphorus exist in the blood stream in a variety of forms, which adds confusion to studies of the metabolism of these substances in normal persons and in persons with rickets, tetany and other diseases.

McLean and Hastings [133] have commented on the fact that the total calcium content of the serum or plasma is nearly all accounted for as calcium ions and calcium bound to protein. While the total calcium content of the serum may fluctuate under normal conditions, especially in response to fluctuations in the concentration of the total protein content of the plasma, the diffusible or ionic calcium is normally maintained within a relatively narrow range by a process of physiologic regulation in which the parathyroid glands play a prominent rôle. Approximately 50 per cent of the calcium content of the serum exists in the ionic or diffusible form, which is the fraction of primary physiologic importance.

While it is clearly recognized that calcium, phosphorus, vitamin D and parathyroid hormone are essential for the mineralization of normal bone and probably play a rôle in the development of rickets and certain other diseases, the rôles played by each individual factor and their interrelationships are not clearly understood. The activity of vitamin D in this respect has been stated to be in the retention of calcium and phosphorus in the body as a whole, in the deposition of calcium and phosphorus in the bones and perhaps in the concentration of these elements in the blood. Early workers in this field suggested that vitamin D in some manner regulates the passage of calcium and phosphorus through the intestinal wall and that therapeutic doses of the vitamin increase the absorption of calcium and phosphorus. Another possible

133. McLean, F. C., and Hastings, A. B.: Clinical Estimation and Significance of Calcium-Ion Concentrations in Blood, Am. J. M. Sc. **189**:601 (May) 1935.

explanation of the retention of calcium and phosphorus which occurs during the administration of vitamin D is the decreased excretion of these elements through the intestinal wall or kidney. The rôle of vitamin D in the deposition of calcium and phosphorus in bone is also uncertain, but it is clearly recognized that in the absence of vitamin D bone is abnormal both in chemical composition and histologic structure. It is possible that some of these metabolic factors are influenced by vitamin D, which may perhaps be called the regulator of the level of calcium in the blood, through stimulation of the parathyroid glands or by rendering the organism more responsive to the hormone.

In this connection the studies of Wilder, Higgins and Sheard [134] are of particular interest, for the authors have demonstrated in the chick that deprivation of vitamin D insufficient in degree to cause rickets will produce hypertrophy and hyperplasia of the parathyroid glands. Other observations that these investigators made are interpreted to mean that the supply of parathyroid hormone determines the sensitivity of the organism to the action of vitamin D. A diminished supply of the hormone, such as may be available after parathyroidectomy, diminishes the ability of the organism to function normally with restricted amounts of D. An augmented supply conditions the tissues of the organisms so that the effects of the vitamin are more intense and so that amounts of vitamin which otherwise would not prevent rickets do prevent it.

The rôle of concentration of calcium and phosphorus in the blood in the mineralization of bone and the part played by vitamin D in such concentration in rickets is questionable. As a result of their recent studies, Compere, McLean and Hastings [135] report that neither the amount nor the state of calcium in the blood serum of rachitic infants is necessarily altered from that in the serum of normal infants. They express the belief, therefore, that the pathologic change in patients with rickets is not on the basis of a change in the amount or state of the calcium in the blood. The effect of vitamin D in increasing the phosphorus content of the serum in patients with rickets may come about as a result of increasing the capacity of the blood to hold phosphorus, possibly by raising the level at which it begins to be excreted.

The immediate rôle of calcium and phosphorus in relation to these metabolic processes is probably more simple than that of vitamin D. In the absence of sufficient quantities of either calcium or phosphorus,

134. Wilder, R. M.; Higgins, G. M., and Sheard, Charles: The Significance of the Hypertrophy and Hyperplasia of the Parathyroid Glands in Rickets and Osteomalacia, Ann. Int. Med. **7**:1059 (March) 1934.

135. Compere, E. T.; McLean, F. C., and Hastings, A. B.: State of Calcium in the Fluids of the Body: II. Calcium in the Blood in Rickets, Am. J. Dis. Child. **50**:77 (July) 1935.

and particularly calcium in assimilable forms, rickets or other abnormality of bone may develop despite an adequate intake of vitamin D and the presence of normal parathyroid glands. As Schmidt and Greenberg point out, the composition of the blood with respect to the calcium and phosphorus, in the last analysis must depend on a balance of their absorption from the ingested food, their excretion by way of the urine and feces and their storage and release from the tissues, more particularly the skeleton.

In the past year certain other observations have been made in regard to the calcium and phosphorus content of the blood and vitamin D, which are worthy of separate report. McLean and Hastings have attempted to simplify interpretations of estimations of serum calcium and diffusible and nondiffusible forms. They express the belief that increases in the concentration of the calcium ion are presumptive evidence of hyperparathyroidism. Decreases in the concentration of the calcium ion occur only as a result of hypofunction of the parathyroid glands or as a result of the hypophosphatemia of uremia. The possible exceptions to these two conclusions may be hypercalcemia from the administration of viosterol in excessive doses and so-called low-calcium rickets, associated with infantile tetany.

Problems in the assimilation and utilization of calcium are presented by Telfer (according to Friedman [136]) and by Kohman and Sanborn.[136b] Telfer points out the interesting fact that the amount of calcium retained by infants who receive whole cow's milk is two or three times greater than that retained by normal infants fed breast milk. Why under such circumstances rickets is more common among bottle-fed babies is uncertain. Kohman and Sanborn have studied the effect of the oxalic acid content of leafy vegetables on the assimilation of calcium. While there is insufficient oxalic acid in these foods to produce toxic effects, the formation of highly insoluble calcium oxalate may interfere with absorption, and oxalate may also interfere with the retention of calcium.

To certain patients who fail properly to absorb lipoid, vitamin D may be administered by the dermal route. The vitamin is satisfactorily absorbed from the skin, and when administered in this fashion it will cure or prevent rickets of experimental animals. Since dermal absorption is variable, the dose required is not clear.

Toxic Effects of Vitamin D.—While there is as yet little information in regard to the quantitative requirements of the vitamins, much

136. Telfer, quoted by Friedman, Samuel: Infant Feeding and Nutrition, Am. J. Dis. Child. **49**:460 (Feb.) 1935.

136b. Kohman, E. F., and Sanborn, N. H., cited in Oxalic Acid and Calcium Utilization, editorial, J. A. M. A. **105**:440 (Aug. 10) 1935.

interest has been aroused over the effects of excessive quantities of them. As emphasized last year, there is not good evidence of such toxic effects except in the case of vitamin D. Much interest has attached itself to this problem in view of the almost universal use among civilized people of various preparations of vitamin D in the treatment of infants and children. Bills has recently reviewed the evidence on this point and has emphasized the fact that the range between the ordinary therapeutic doses of vitamin D and the dose which produces adverse symptoms is extraordinarily wide. This is fortunate, because probably no potent substance enters the bodies of animals in more variable amounts than does vitamin D. Bills suggests that the production of toxic effects depends on the daily dose, the duration and the route of administration, the calcium and phosphorus content of the diet, the age and activity of the subject, the individual susceptibility, the susceptibility of the species and other factors. The lethal dose of vitamin D for man is unknown. Reed's [137] daily dose given to patients who had hay fever amounted to about 2,760,000 international units (equivalent in rat units to 30 liters of cod liver oil). While this dosage caused some patients to have unpleasant symptoms, there were no serious effects. When Spies and Hanzel [138] administered more than 18,000,000 international units daily, hypercalcemia was produced, but pathologic calcification of the tissues was not observed.

Bills lists the following warning symptoms of toxic action of vitamin D: a sense of well-being and increased appetite changing to nausea, anorexia, vomiting, cramps, diarrhea, frequent urination, sometimes neuralgia along the course of the mandibular branch of the trigeminal nerves, tenderness of the teeth and gums, pain in the muscles and joints, dizziness, muscular weakness, headache and haziness of memory.

DENTAL CARIES

Great interest has been displayed in recent years in the dependence of normal development of the teeth on adequate nutrition and in the relationship between dietary deficiency and dental caries. Since dental caries is found predominantly among civilized peoples, much study has been given to the dietary differences which exist between civilized and uncivilized peoples. Discovery of the vitamins and of the importance of calcium and phosphorus has precipitated such investigations and has added much information about normal dentition, which should be of

137. Reed, C. I.: Symptoms of Viosterol Overdosage in Human Subjects, J. A. M. A. **102**:1745 (May 26) 1934.

138. Spies, T. D., and Hanzel, R. F.: Experimental Production of Hypercalcemia in Human Beings by Means of Irradiated Ergosterol, Proc. Soc. Exper. Biol. & Med. **31**:747, 1934.

great value in the prophylaxis of dental caries. That caries is a matter of great importance from the standpoint of public, as well as of individual, health is well illustrated by the fact that a survey made in 1934 by the British Dental Association [139] revealed that of 3,000,000 children, 60 per cent had defective teeth and needed treatment.

At present there are two schools of thought in the study of dental caries. According to Bunting,[140] the first school holds the view that the most important consideration is the environment of the teeth (bacterial flora, carbohydrates, acids formed in the mouth and films and plaques over the teeth which may protect the acids of caries from dilution and neutralization). The second school contends that the perfection of the tooth itself and its resistance to the attacking force are most important. Both groups agree that diet is closely associated with dental caries and that at present the most efficient known preventive measures against dental disease are dietary.

The various factors in diet which have been considered important in dental caries include calcium, phosphorus, carbohydrate and vitamins A, C and D. It is recognized also that the mechanical state of the food is significant. As one cause for confusion in this problem, Schmidt and Greenberg point out that too much emphasis has been placed on the metabolism of each individual element rather than consideration to the subject in its entirety. Nevertheless, brief discussion will be given to the rôle played by the mentioned factors.

Calcium and Phosphorus.—Since 97 per cent of the inorganic salts found in enamel and 62 per cent of those found in dentin are made up principally of calcium phosphate, it is obvious that these elements are essential in the development of normal teeth. However, numerous studies indicate that a deficiency of calcium and phosphorus is not of any moment in determining hypoplasia of the enamel or increased susceptibility to caries. The work of Boyd, Drain and Stearns [141] on the retention of calcium and phosphorus showed that the highest retention of calcium and phosphorus was noted among children whose teeth gave evidence of inactive decay and that the least retention was found among those who gave evidence of active caries. Retention among those children who had no caries averaged approximately 50 per cent higher than among those who had active caries, despite the fact that among the latter retention was as high as, or higher than, that usually accepted as normal.

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139. The Prevalence of Dental Disease, London letter, J. A. M. A. **104**:2277 (June 22) 1935.

140. Bunting, R. W.: Diet and Dental Caries, J. Am. Dent. A. **22**:114 (Jan.) 1935.

141. Boyd, J. D.; Drain, C. L., and Stearns, Genevieve: Metabolic Studies of Children with Dental Caries, J. Biol. Chem. **103**:327 (Dec.) 1933.

Carbohydrate.—The rôle of carbohydrates in the production of dental caries is highly disputed. Some investigators are of the opinion that a diet high in carbohydrate, leading to marked increase in the Bacillus acidophilus content of the saliva, is a factor of great significance in the develpoment of dental caries. Bunting suggests that thus far between persons free from caries and persons susceptible to caries the only observed differential characteristic offering a high degree of correlation is the relative number of B. acidophilus organisms in the mouth. Those who belong to the group who believe in the theory that the perfection and resistance of the tooth itself are the most important factors in resisting dental caries are under the impression that the rôle of bacteria in the control of caries seems to be secondary. Consequently, if the diet is adequate in those substances which are required in normal nutrition, caries will be controlled or arrested. Bunting summarizes the problem by saying that the manner in which, and the extent to which, sugar enters into the problem of dental caries is not as yet apparent.

Vitamin A.—Vitamin A is not clearly an essential for normal dental development. May Mellanby [142] is of the opinion that this vitamin is significant in the development of the gingival epithelium and that deficiency of this factor may therefore favor the development of pyorrhea.

Vitamin C.—The importance of vitamin C in dental caries was first emphasized by Howe.[143] It has been demonstrated that changes in the teeth of guinea-pigs occur at an early stage of deficiency of vitamin C and afford the surest clinical sign of scurvy in its latent stages. Hanke [144] produces evidence to suggest that a pint of orange juice should be taken every day to provide adequate amounts of vitamin C in preventing and healing dental caries, but against this is a wide variety of carefully collected clinical observations. The immediate rôle of vitamin C in dental development is in the maintenance of normal functional activity and prevention of premature degeneration of odontoblasts and cementoblasts.

Vitamin D.—To the Mellanbys [145] must go credit for emphasizing the rôle of vitamin D in dental caries. In their opinion it is the most

142. Mellanby, May: Diet and the Teeth: An Experimental Study: II. A. Diet and Dental Disease; B. Diet and Dental Structure in Mammals Other Than the Dog, Medical Research Council, Special Report Series, no. 153, London, His Majesty's Stationery Office, 1930.

143. Howe, P. R.: Investigations of Dental Caries, J. Am. Dent. A. **14**:1864 (Oct.) 1927.

144. Hanke, M. T.: The Rôle of Diet in the Cause, Prevention and Cure of Dental Disease, J. Nutrition **3**:433 (Jan.) 1931.

145. Mellanby, Edward: Nutrition and Disease: The Interaction of Clinical and Experimental Work, London, Oliver & Boyd, 1934. Mellanby.[142]

important protective factor available in the diet. Much controversy still exists in regard to the indispensability of vitamin D in the prevention and healing of dental caries. The frequent lack of relationship between caries and rickets is emphasized in this connection. Others [146] have produced evidence that dental caries may exist although there is no lack of vitamin D during the development of teeth and that decay may continue although large doses of vitamin D are being administered. The rôle of vitamin D, calcium and phosphorus in relation to dental development will be considered in the paragraphs on rickets.

Fineness and Coarseness of Food.—Hoppert, Webber and Canniff [147] have demonstrated that fineness of division of food is more important than quality in the production of dental caries of rats. They were able to produce caries at will by feeding adequate diets of food coarsely ground which did not produce caries when the food was finely ground.

In summarizing, Bunting states: "(1) In a small percentage of cases, inherited tendencies or inherent characteristics may be more important factors in caries susceptibility than any ordinary dietary consideration. (2) In the majority of cases dental caries will be definitely arrested by the adoption of a simple, fairly adequate, low sugar diet. (3) No constant relationship could be found between the degree of activity of dental caries and the amounts of calcium phosphorus, vitamin D or C, or the acid base value in the diet, or in the blood or saliva." It is of interest to note that while Bunting expresses the opinion that diet controls dental caries through determination of the environment of the teeth and Drain and Boyd [148] are firmly convinced that endogenous factors are responsible primarily for the control and the arrest of dental caries, nevertheless the diets advised by these two opposing groups are essentially the same. A sample diet (Drain and Boyd) for a child from 5 to 16 years of age would consist of 1 quart (946 cc.) of milk; at least one egg; one serving of meat, fish, chicken or liver; two vegetables, one-half cup of each; one orange, apple or tomato and one additional fruit; 1 teaspoonful of cod liver oil, and 6 teaspoonfuls of butter. Large quantities of sugar are better omitted.

IRON AND COPPER

Perhaps the most interesting report in relation to hemoglobin and iron metabolism during the past year is that of Whipple,[149] in his Nobel

146. Hansman, F. S., and Marshall, F.: The Etiology of Dental Caries, M. J. Australia **2**:511 (Oct. 20) 1934.

147. Hoppert, C. A.; Webber, P. A., and Canniff, T. L.: Production of Dental Caries in Rats Fed an Adequate Diet, J. Dent. Research **12**:161 (Feb.) 1932.

148. Drain, C. L., and Boyd, J. D.: Endogenous Factors in the Control and Arrest of Dental Caries, J. Am. Dietet. A. **10**:471 (March) 1935.

149. Whipple, G. H.: Hemoglobin Regeneration as Influenced by Diet and Other Factors, J. A. M. A. **104**:791 (March 9) 1935.

prize lecture, entitled "Hemoglobin Regeneration As Influenced by Diet and Other Factors." In this report he summarizes the experience of his colleagues and himself in demonstrating the value of various factors in the regeneration of hemoglobin of dogs rendered anemic at constant levels by suitable removal of new-formed hemoglobin. Liver stands out as the most potent dietary factor, with kidney a close second and thereafter gizzard, spleen and pancreas. Iron was found to be the most potent inorganic element. The potency of human liver compared with that of standard animal liver was of interest. That of young, healthy adults obtained at necropsy gave average values of 160 per cent (compared with those of pig liver, 100 per cent). Liver tissue from elderly persons who had arteriosclerosis and degenerative changes gave a value of 117 per cent. That of persons with chronic infections and cirrhosis gave about normal values except when hepatic insufficiency intervened; then the values fell to 48 per cent (one-third that of normal human liver). In persons with pernicious and aplastic anemia the values ran to more than 200 per cent.

The dependence of anemia of man on nutritional deficiency is emphasized by Minot. He points out that there are three classes of dietary substance the lack of which leads to anemia: 1. Lack of iron leads to the formation of microcytic and hypochromic erythrocytes. 2. Lack of vitamin C leads to the formation of normocytic or slightly macrocytic erythrocytes. 3. A mysterious substance is contained abundantly in liver, the absence of which leads to pernicious anemia. From the clinical standpoint, Minot calls attention to the rôle which may be played by infection, increased or altered metabolism, arteriosclerosis or serious damage to vital organs in precipitating the person who is receiving "just enough" iron into one of the states of anemia mentioned.

There has always been much discussion of the requirement of iron by the normal adult and the effect of insufficient quantities of iron on the development of anemia. In the past few years the availability of iron which occurs in foods has been shown to be of great significance. Recent studies by Farrar and Goldhamer,[150] if confirmed, may force a revision of some conceptions in regard to the requirement of this element. During a study of balance carried out on a man over a longer period of time than usual, these workers were able to maintain the iron balance with an intake of 4.9 mg. daily, and the blood, that is, the hemoglobin and iron content and the erythrocyte count, remained normal during the time over which the mentioned intake was continued. The authors are inclined to the opinion that the iron requirement of the

150. Farrar, G. E., Jr., and Goldhamer, S. M.: The Iron Requirement of the Normal Human Adult, J. Nutrition **10**:241 (Sept. 10) 1935.

normal man is not more than 5 mg. daily. The normal excretion of iron in the urine was found to amount to 0.02 mg. for each 100 cc.

An exceedingly important conception is that which Elvehjem, Hart and Sherman [151] present on the availability of iron in many foods, that is, the proportion of the total iron content of a food which the gastrointestinal tract and the organism are able to utilize. Naturally, the amount of available iron is more important than the total iron content of the diet. Hematin iron apparently is not utilized by the digestive tract. In the aforementioned studies of balance of Farrar and Goldhamer, of the 5 mg. of iron given daily, only 3 mg. was in the available form.

Some very interesting studies of nutritional anemia have been reported in the past year. Results of scientific studies are rapidly revising ideas in regard to the etiology and treatment of this exceedingly common condition in infancy. Davidson, Fullerton and Campbell [152] report that this type of anemia is of relatively infrequent occurrence and of minor clinical importance (except at two age periods: in infants between the eleventh and the twenty-third month of life and among women). In women pregnancy and menstruation are probably significant contributing etiologic factors. In their studies of 3,500 persons in Aberdeen these investigators found anemia in the following groups: 41 per cent of infants less than 2 years of age, 32 per cent of children of school age, 2 per cent of school children and 45 per cent of women.

While the normal full term infant is usually born with large stores of iron, the premature baby is frequently anemic. The main mechanisms which may be concerned in the development of the anemia of prematurity are said to be deficient antenatal storage of iron or possibly of copper or of some other essential hematogenic substance, and perhaps deficient formation of blood attributable to hyperplasia of marrow or to increased destruction of blood. According to editorial comment in *The Journal of the American Medical Association*,[153] most evidence favors the latter view, although it is not certain.

In the treatment of nutritional anemia, which is a normal phenomenon in infancy, Usher, McDermot and Lozinski [154] report that the

151. Elvehjem, C. A.; Hart, E. B., and Sherman, H. C.: The Availability of Iron from Different Sources for Hemoglobin Formation, J. Biol. Chem. **103**:61 (Nov.) 1933.

152. Davidson, L. S. P.; Fullerton, H. W., and Campbell, R. M.: Nutritional Iron-Deficiency Anemia, with Special Reference to Prevalence and Age and Sex Incidence, Brit. M. J. **2**:195 (Aug. 3) 1935.

153. Anemia of Premature Infants, editorial, J. A. M. A. **104**:565 (Feb. 16) 1935.

154. Usher, S. J.; MacDermot, P. N., and Lozinski, E.: Prophylaxis of Simple Anemia in Infancy with Iron and Copper: Effect on Hemoglobin, Weight and Resistance to Infection, Am. J. Dis. Child. **49**:642 (March) 1935.

addition of fruit, vegetables and cereals is not a preventive factor and that the administration of iron in doses of 1.5 to 3 Gm. daily was not as effective as when the iron was combined with from 1/60 to 1/32 grain (0.0011 to 0.002 Gm.) of copper daily. It was also observed that infants so treated with iron and copper had a definite advantage in lessened incidence and severity of infection as well as in a lower mortality. Mackay [155] reports similar but more striking results.

Although it is difficult to demonstrate the rôle of copper in forms of anemia other than the nutritional variety, copper apparently plays an essential rôle in the formation of hemoglobin. Chou and Adolph's [156] studies on copper balance showed the copper requirement of man to be about 2 mg. daily. This element, which is excreted chiefly in the feces, also appears in the urine at fairly constant levels (average, 0.25 mg. daily). Copper, which occurs in the blood in larger than normal quantities in many forms of anemia, is stored principally in the liver, muscle and bones.

155. Mackay, Helen M. M., quoted by Usher, MacDermot and Lozinski.[154]

156. Chou, T. P., and Adolph, W. H.: LIV. Copper Metabolism in Man, Biochem. J. **29**:476 (Feb.) 1935.

Book Reviews

Working Test as a Clinical Method for Determining the Function of the Lungs: An Investigation in Cases of Tuberculous Changes Especially in Collapse Therapy. By I. L. Bluhm. Supplement LXV, Acta Medica Scandinavica. Pp. 209, with 5 illustrations and 78 tables. Stockholm: P. A. Norstedt & Söner, 1935.

As a preliminary to his main work Bluhm has investigated the basal metabolism and the minute volume of cardiac output in tuberculous patients. The body of the report deals with a functional test of the lungs and a comparison with readings for vital capacity in the same cases. The history, technic and material are discussed under each heading. Brief histories of all the patients are given, and results are tabulated in detail and with numerous charts.

In determination of the standard metabolism, the oxygen consumption was measured with Krogh's apparatus and converted by use of the tables of Harris and Benedict, using plus 15 per cent as the upper limit of normal. In 40 ten minute and 411 five minute tests on a variety of tuberculous patients, some under treatment by different types of collapse therapy, Bluhm found a normal standard metabolism independent of the activity, the extension and the clinical nature of the process. In 36 cases no parallelism was found between the basal metabolic rate and the sedimentation reaction. Even in cases in which minor elevations of temperature were present, the standard metabolism was normal.

The minute volume of cardiac output was determined by the acetylene method of Grollman on 35 tuberculous patients, 20 of whom had some degree of collapse of the lung. In all the patients except 1 with severe pulmonary changes normal values were found for minute volume, utilization and stroke volume. Bluhm found the method not applicable in cases in which the vital capacity was 1.5 liters or less.

The study of the function in tuberculous lungs was made by the following method, which has been used by Nylin in cardiac diseases: A five minute curve of oxygen consumption is obtained under standard conditions. Immediately following the patient starts walking up and down three sets of stairs (three steps up and three steps down in each set) arranged in a circle, at a rate of eighty-eight steps per minute paced by a metronome. After twenty rounds (occasionally only ten rounds when the patient became easily short of breath) he reclines on a sofa, and forty-five seconds after the cessation of work a second curve of oxygen consumption is started and continued for four minutes. The percentage increase in oxygen consumption per minute after work is calculated and referred to as the relative oxygen debt. In 67 tests on 31 normal persons the relative oxygen debt was practically always between 10 and 25 per cent for either ten or twenty rounds. The maximum variation in repeated tests on the same subject was 6 per cent. The test was applied to 102 tuberculous patients mostly between the ages of 20 and 30. A total of 411 tests were made. A relative oxygen debt of more than 25 per cent is considered abnormal, and the term respiratory insufficiency is used to describe the condition in cases in which such values obtain. Eight of 43 patients without operative intervention showed respiratory insufficiency which could be explained usually by the extent of the pulmonary lesions. Tests were made on patients under pneumothorax treatment before and after a refill with nitrogen gas. In 10 of 32 tests there was an increased relative oxygen debt. The increase was dependent on the degree of respiratory insufficiency present and the amount of gas injected. There were no increased values in cases in which the relative oxygen debt was below 35 per cent before a refill, even when 800 cc. of gas was added. Usually by the second, and practically always by the third, morning after the refill the values had returned to those present before insufflation.

Of 43 patients with unilateral pneumothorax, 33 showed a relative oxygen debt above 25 per cent. In all cases in which collapse was effective there was an increase in the relative oxygen debt following the induction of pneumothorax. The degree of respiratory insufficiency was dependent on the degree of collapse and the type and extent of the original tuberculous process. The following tendencies were noted on smaller groups of patients: There was a greater degree of respiratory insufficiency in cases of unilateral pneumothorax in which the other lung had previously been treated with gas than in simple unilateral pneumothorax. In seropneumothorax the change in the relative oxygen debt is dependent on an increase or a decrease in the amount of exudate, other factors being the same.

A comparison of vital capacity and relative oxygen debt is made. In general, there is an abnormal decrease in vital capacity in cases in which there is an abnormal increase in the relative oxygen debt. However, Bluhm believes that there is more individual variation in readings for vital capacity and that the increased value of the relative oxygen debt is more sensitive as an indicator of the type of condition which causes clinical dyspnea. One senses that he regards vital capacity more as an anatomic measure and relative oxygen debt more as a physiologic measure of respiratory function.

An attempt is made to correlate the present working capacity of the patients and the findings of the relative oxygen debt. There may be some doubt as to the final value of such comparison, in view of the relatively short time which has elapsed, the difficulty of evaluating working capacity and the uncertainty of the course of pulmonary tuberculosis. However, Bluhm thinks that there is good correspondence between the results of the functional test and the present working capacity of the patients, even if one ignores the clinical changes.

A large amount of work is represented in this investigation, and one feels that the conclusions are in the main fairly drawn. As to the possible clinical application of the method, it would be difficult to make a forecast. The procedure would seem to offer an objective measure of the tendencies which express themselves clinically by the development of dyspnea.

Ueber Sternalpunktionen. By Elsa Segerdahl. Acta Medica Scandinavica, Supplementum LXIV. Pp. 162, with 16 illustrations. Uppsala: Appelbergs Boktryckeriaktiebolag, 1935.

This monograph presents a thorough and extensive investigation of the aspiration method (Arinkin) of obtaining bone marrow for biopsy. The literature is thoroughly reviewed. The experiments of other investigators were painstakingly repeated. One hundred and ten normal persons and seventy-five persons with pathologic conditions were studied.

The simplicity of this technic commends itself for clinical use (an article describing an almost identical technic of bone marrow puncture appeared in a recent issue of the ARCHIVES OF INTERNAL MEDICINE **55**:186 [Feb.] 1935). The loss of structural relationships in the marrow so removed is the only limitation of the method that does not apply to other methods of obtaining marrow for biopsy. In this method, as in others, there is an indeterminable admixture of peripheral blood and specific bone marrow elements. Segerdahl confirms the findings of Tuschinsky and Kotlarenko that the greater the amount of material aspirated the greater the dilution with blood. The withdrawal of 0.2 cc. of material is recommended.

Differential counts of the aspirated material are of questionable value, as the variability is too great. The findings of an unusually high or low cell count (from 70,000 to 80,000 per cubic millimeter was the average leukocyte count) or of diseased cells are of greater significance.

Aleukemic leukemia was the only condition in which the method was found to be of distinct diagnostic value. During severe remissions in cases of pernicious anemia a characteristic and diagnostic increase in megaloblasts in the marrow was found. However, the method is of no value in mild remissions or in patients

treated with liver. Segerdahl points out that a change from a megaloblastic marrow to a normoblastic marrow begins within twenty-four hours after the institution of the parenteral administration of liver. Therefore the potency of a liver preparation may be judged more rapidly by this method than by any other. The criterion, however, is purely qualitative.

The Principles and Practice of Medicine. By Sir William Osler. Twelfth edition. Revised by Thomas McCrae. Price, $8.50. Pp. 1196, with 22 illustrations. New York: D. Appleton-Century Company, Inc., 1935.

"The Principles and Practice of Medicine" of Sir William Osler, the textbook for medicine used in the instruction of nearly all today's practitioners when they were students, has been continuously revised and reedited since the death of Osler by his former associate, Thomas McCrae. The reviewer, as he scans these pages, is reminded vividly of the copy of that earlier edition, read through more than once, forward and backward, in preparation for those recitations and examinations that then seemed so richly pregnant with distressing possibilities. The fresh clean pages of this new book contrast strangely with those of the old. They were covered with marginal notes of the gems of wisdom that fell from the lips of the old professors. They were illuminated also with red lines which underscored those passages intended to be stamped indelibly on the memory and by occasional puns or raw anatomic jokes and pictures, here and there, of this or that outstanding and usually peculiar character of some classmate or teacher. These pages are fresh and new, but what is more to the point, they are completely up to date.

The style of the old master has been retained remarkably—the opening chapter on typhoid fever is very little changed from what it was when Osler wrote it, but what a lot of information has been added! New diseases appear; some grow less important, while others disappear, as is written by McCrae in his interesting preface. There are changes and additions in this last revision in practically every part of the book. Certain sections are new or have been altered materially. A long list of these is given; among them are the divisions on undulant fever, psittacosis, hypoglycemia, agranulocytosis and fifty others.

There is much to be said for a textbook of medicine written, as is this, by a single author. The number of physicians today who are qualified to attempt such a task is small, and yet it is true, as is stated by McCrae, that the splitting of internal medicine into separate compartments tends to emphasize the study of one part without sufficient attention to the fact that patients are individuals and are made up of many systems. "Too often the idea is held that a clinician can be made . . . with the aid of instruments and laboratory procedures. . . . Time, effort, and hard work must go to the acquiring of a knowledge of disease. We cannot be Osler's, but we can do our best to follow his footsteps." The physician and student should learn everything possible about the patient by the use of his senses and brains before turning to the laboratory, and, so far as possible, a textbook of medicine should emphasize the clinical side of the problems of disease. This policy has been followed conscientiously in the preparation of the successive editions of the Osler text.

Tuberculosis. By Dr. Fred G. Holmes. Price, $2. Pp. 312. D. Appleton-Century Company, Inc., 1935.

This volume is a valuable addition to the list of books that are designed as guides for patients suffering from pulmonary tuberculosis. It is written by one who is recognized as an authority and epitomizes his long clinical experience in the diagnosis and treatment of tuberculosis. It is comprehensive enough to cover all the important subjects on which the patient requires information during the long course of his illness and is written with such simplicity that he can understand the purpose of the treatment and intelligently cooperate with the medical adviser. The book, because of the discussion of the methods of treatment, will

be found of great value to the practicing physician who has had less experience in the care of the tuberculous patient. Few authors have made a more frank statement of the value of climate. The six principles laid down rationalize decisions regarding the advisability of seeking climatic change and properly remove from the subject of climate the romantic values that have existed in the optimistic minds of physicians and patients alike.

Of no less value are the equally frank discussions of the employment and continued use of artificial pneumothorax and of the surgical procedures that are now commonly resorted to in treatment. The indications for each method of treatment are outlined, and the advantages of each method are balanced against the disadvantages. Technic is discussed only briefly; Holmes is more interested in the final result.

The book will be of great value to the patient because of the simplicity and clarity of its style. The thoughtful tuberculous person cannot fail to be impressed with the necessity of an exact diagnosis and cannot be ignorant of the facts that must be assembled to make accuracy possible. The patient is made to understand the importance of the presence of a lesion discovered by physical or by roentgenologic examination and the confirmation of its nature by the discovery of Mycobacterium tuberculosis. He is led to minimize the relative importance of such common subjective symptoms as fatigue and fever in the absence of objective evidence. After the establishment of an accurate diagnosis, he is informed of the nature of the disease and its symptoms and complications and of his responsibilities both to himself and to those with whom he comes in contact. Moreover, he is left in no doubt about the importance of every method of treatment and of the advantages that are to be expected from each. The book lays down the fundamental principles of the cure of tuberculosis and stimulates the intelligent cooperation of the patient in the treatment advised and employed.

The Medicine Man of the American Indian and His Cultural Background. By William Thomas Corlett, M.D., L.R.C.P. (Lond.), professor emeritus of dermatology-syphilology, Western Reserve University; Fellow of the Royal Society of Medicine of Great Britain; Fellow of the American Medical Association; honorary member and sometime president of the American Dermatological Association; corresponding member of the British Association of Dermatology and Syphilology; Fellow of the American Association for the Advancement of Science. Price, $5. Pp. 327, with 24 illustrations. Springfield, Ill.: Charles C. Thomas, Publisher, 1935.

This delightful work will entertain and instruct all who may read it. It deals with the origin of the American Indian and his migration from Alaska to the tip of South America. It touches on his culture and the development of his civilization and describes the widely differing degree of cultural advancement among the various tribes.

Into this cultural background steps the "medicine man." He was doctor and priest, soul-saver and body-poisoner, wise counselor and, sometimes, not so wise.

It is generally assumed that the medicine man was somewhat of a charlatan and a quack. Corlett points out that nothing could be further from the truth. There were such persons, just as there are today, but the majority were earnest, studious men whose knowledge and practice might be favorably compared with any in a similar state of scientific advancement. They were carefully chosen, spent much time in study and preparation and devoted their lives to their profession. There were outstanding men among them, just as our own race has its prominent figures. It is pointed out that the practice of medicine among these people was surrounded by greater hazards at that time, not only for the patient but also for the practitioner.

Corlett deals with the different diseases that were encountered in the various localities. He touches on fractures and traumatic surgery among the Indians. There is a discussion of obstetric procedure. The pharmacopeia of the Indian has been studied. There is further argument about the origin of syphilis.

In concluding his preface the author states: "I might add this is not a medical book. It has as much religion as medicine, and more theology than pathology. If it were not so it would not be a true account of the medicine-man of the American Indian." Whether or not it is a medical book, it is most interesting reading for the physician—and for any one else who wishes to indulge a taste for browsing in prehistoric material.

Chirurgie de l'oesophage. By Raymond Grégoire, professeur à la Faculté de Médecine de Paris, Chirurgien des Hôpitaux. Price, 35 francs. Pp. 180, with 31 illustrations. Paris: Masson & Cie, 1935.

This monograph on surgery of the esophagus adequately presents the practically important present knowledge concerning the commonly encountered esophageal lesions. Advances in diagnosis and new conceptions of the incidence of certain diseases of the esophagus gained through improved methods of study, such as esophagoscopy, roentgen examination and biopsy, are discussed, and the modern methods of endoscopic and operative treatment are described.

Peptic ulcer of the esophagus is presented as a lesion occurring more frequently than is generally realized. The method of treating this condition is discussed, with special reference to the topical application of silver nitrate solution. In the chapter on esophageal diverticula the methods of diagnosis are well presented. The outline of treatment includes the description and recommendation of a one-stage operation suggested by the author. The theories concerning the etiology of mega-esophagus are presented, and in addition to a consideration of diagnosis, the various methods of dilation and plastic operation applicable in the treatment of this condition are discussed.

The chapter on foreign bodies includes a listing of the indications for approach by esophagoscopy or gastrostomy. Complications, such as perforation, hemorrhage and abscess formation, are described. Grégoire laments the lack of progress in the treatment of cancer of the esophagus. The danger incident to dilation or the implantation of radium in cases of esophageal cancer is shown to detract from the value of these palliative measures. Throughout the book there are pertinent observations on surgical anatomy and pathology. In the last chapter the author outlines the operative approaches and procedures which are available in the surgical treatment of diseases of the esophagus. He is optimistic in regard to the feasibility and good results obtainable through anterior thoracic esophagoplasty.

The book contains thirty-one illustrations, including reproductions of roentgenograms, sketches of operative procedures, photographs of specimens and esophagoscopic images.

Physical Diagnosis. By Warren P. Elmer and W. D. Rose. Seventh edition. Price, $5. Pp. 919, with 342 illustrations. St. Louis: C. V. Mosby Company, 1935.

The teaching of physical diagnosis has always been a problem. As a separate discipline its origins go back a hundred years to Laënnec, Auenbrugger and Skoda. But gradually the technical methods, no longer a novelty, have been more and more absorbed into diagnosis in a broad sense. Most physicians eventually relearn physical diagnosis after years of practice, because the methods work only when used by one sensitive to the problems of disease who more or less knows what he is looking for. The reviewer predicts that as time goes by less and less emphasis will be placed on teaching physical diagnosis as such; this will be learned as an integral part of the general examination and study of patients. Meanwhile it may be said that this book is an excellent exposition of the subject according to present-day standards. As a matter of fact, as its size testifies, it goes somewhat beyond the bounds of the usual compendium of physical diagnosis. The exposition is clear, and the illustrations are excellent.